The effect of exercise training on intrahepatic triglyceride and hepatic insulin sensitivity: a systematic review and meta-analysis

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List of Abbreviations (in order of mention in the paper):

IHTG – intrahepatic triglyceride

NAFLD – non-alcoholic fatty liver disease

T2DM – type 2 diabetes mellitus

DAG - diacylglycerol

EGP – endogenous glucose production

US – ultrasound

CT – computed tomography

^{1}H-MRS – proton magnetic resonance spectroscopy

HISI – hepatic insulin sensitivity index

%EGP_{supp} – percentage suppression of endogenous glucose production during low dose insulin infusion

RCT – randomised controlled trial

HIRI – hepatic insulin resistance index

FPI – fasted plasma insulin

95% CI – 95% confidence interval

HIIT – high-intensity interval training

Abstract

This systematic review and meta-analysis determined the impact of structured exercise training, and the influence of associated weight loss, on intrahepatic triglyceride (IHTG) in individuals with non-alcoholic fatty liver disease (NAFLD). It also examined its effect on hepatic insulin sensitivity in individuals with or at increased risk of NAFLD. Analyses were restricted to studies using magnetic resonance spectroscopy or liver biopsy for the measurement of IHTG and isotope-labelled glucose tracer for assessment of hepatic insulin sensitivity. Pooling data from 17 studies (373 exercising participants), exercise training for one to 24 weeks (mode: 12weeks) elicits an absolute reduction in IHTG of 3.31% (95% CI: -4.41 to -2.22%). Exercise reduces IHTG independent of significant weight change (-2.16 [-2.87 to -1.44]%), but benefits are substantially greater when weight loss occurs (-4.87 [-6.64 to -3.11]%). Furthermore, meta-regression identified a positive association between percentage weight loss and absolute reduction in IHTG (β = 0.99 [0.62 to 1.36], P<0.001). Pooling of six studies (94 participants) suggests that exercise training also improves basal hepatic insulin sensitivity (mean change in hepatic insulin sensitivity index: 0.13 [0.05 to 0.21] mg•m^{-2}•min^{-1} per μU•mL^{-1}), but available evidence is limited and the impact of exercise on insulin-stimulated hepatic insulin sensitivity remains unclear.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide (1) and a prominent risk factor for cardiovascular disease, chronic kidney disease and type 2 diabetes mellitus (T2DM) (2). Insulin resistance promotes hepatic lipid accumulation, which is most commonly assessed via the measurement of intrahepatic triglyceride (IHTG) (3–6). The associated accumulation of lipid intermediates, such as diacylglyerol (DAG), may in turn perpetuate insulin resistance (3–6); providing a mechanistic link between NAFLD and impaired metabolic regulation. As such, strong associations exist between excess IHTG and insulin resistance in multiple tissues, including the liver (3,7,8). Defects in hepatic insulin signalling contribute to elevated endogenous glucose production (EGP) which is integral to the pathophysiology of impaired glucose regulation and T2DM (6,9,10).

Prompted by reports that exercise training has the capacity to reduce IHTG in the absence of weight loss (11,12), the independent effects of exercise in the treatment of NAFLD have been examined (13–17). These reviews confirm the ability of exercise to reduce IHTG without significant weight change; however, the importance of the exercise-related energy deficit and subsequent weight loss has not been investigated thoroughly. Acute and sustained energy restriction and weight loss potently reduces IHTG in individuals with NAFLD (18,19) and therefore logic dictates that weight loss associated with exercise training would be an important mediator of the IHTG response to exercise training. This issue has practical implications for the prescription of exercise in the management of NAFLD and thus deserves explicit attention.

Previous reviews highlight a range of different methods to estimate IHTG, including non-invasive imaging by ultrasound (US) or computed tomography (CT), proton magnetic resonance spectroscopy (^{1}H-MRS) and invasive liver biopsy. The inclusion of multiple methods within these reviews has the benefit of broadening study eligibility and thus increasing pooled participant sample size. However, it also adds an additional source of heterogeneity. US and CT are also limited by a lack of sensitivity to detect mild-to-moderate accumulation of IHTG and to quantify subtle changes resulting from experimental interventions (20). ^{1}H-MRS has much greater precision (21), making it a more suitable method for experimental research, whilst the necessity to characterise histological features beyond steatosis make liver biopsy the standard tool in clinical practice (22,23).

The effect of exercise training on hepatic insulin sensitivity has not been reviewed. A number of indices exist which assess insulin resistance using simple circulating biomarkers (24) but stable or radioactive isotope-labelled tracers are required to obtain the most accurate measurement of insulin sensitivity in individual tissues (25). Glucose tracers can be used to quantify EGP (primarily attributed to hepatic glucose production) (10) to accurately assess hepatic insulin sensitivity in the basal (fasted) and insulin-stimulated (post-prandial) states; using the hepatic insulin sensitivity index (HISI) and percentage suppression of EGP ($\%EGP_{supp}$) by low-dose insulin infusion, respectively (24,26).

This systematic review and meta-analysis had two primary aims. First, we investigated the effects of structured exercise training on IHTG in individuals with NAFLD, with a particular focus on the impact of concurrent weight loss, whilst restricting analyses to studies using ^{1}H-MRS and liver biopsy. Second, we explored the effects of exercise training on basal and insulin-stimulated hepatic insulin sensitivity.

Methods

The current systematic review and meta-analysis (PROSPERO ID: CRD42014007268) was conducted in accordance with the "Cochrane handbook for systematic reviews of interventions" and PRISMA guidelines (27,28). All aspects of the literature search, study selection and risk of bias assessment were completed by two researchers independently (JS and JK/SW). Data extraction and analysis were performed by a single researcher (JS) before being checked, independently, by another (extraction: JK; analysis: DB/LG).

Primary outcomes

This review had two outcome measures:

- IHTG
- Hepatic insulin sensitivity (basal and insulin-stimulated)

Eligible studies were restricted to those using ^{1}H-MRS or liver biopsy for the measurement of IHTG, and using isotope-labelled glucose tracer to quantify EGP in the fasted state and following low-dose ($\leq$ 20 mU•m^{-2}•min^{-1} or $\leq$ 0.5 mU•kg^{-1}•min^{-1}) insulin infusion, for the calculation of HISI and %EGP$_{supp}$, respectively.

Literature search

Six electronic online databases (EMBASE, MEDLINE, PubMed, Scopus, Sport Discus and Web of Science) were searched from inception to July 2017 using terms related to exercise, IHTG and hepatic insulin sensitivity. The full list of search terms can be found in supplementary methods. Reference lists of all included manuscripts were screened for further eligible studies.

Study selection

Human experimental studies written in the English language were included. Conference abstracts were considered but underwent the same eligibility and risk of bias assessments as full articles. Eligible studies were those in which participants with overweight or obesity completed an exercise training programme of at least three exercise sessions. All types of study design were considered. Studies investigating changes in IHTG were only eligible if participants had diagnosed NAFLD or where baseline characteristics met diagnostic criteria (IHTG > 5% in the absence of secondary steatogenic sources, including excessive alcohol intake and viral infection (22,23)). NAFLD was not an inclusion criterion for studies investigating changes in hepatic insulin sensitivity as it became apparent that very few studies have examined this outcome exclusively in this patient group and a number of otherwise eligible studies did not measure IHTG. Studies investigating exercise in combination with dietary intervention were eligible only when data were available for matched, independent groups prescribed exercise training with or without diet. In studies measuring hepatic insulin sensitivity, it was essential that participants refrained from strenuous exercise for at least 48 hours before assessments (29).

Data extraction

Descriptive information (first author and year of publication), details of study design, participant and intervention characteristics and outcome data were extracted from eligible manuscripts. Outcome data were extracted as mean change and standard deviation from pre- to post-intervention for all exercise groups, as well as for the control groups of randomised controlled trials (RCTs). Where possible, outcome data presented in alternative forms were converted as outlined in supplementary methods. When incomplete or insufficient data were reported, the authors were contacted. If the required data were unavailable the study was

removed. When characteristics of exercise interventions (such as the frequency, intensity or duration of exercise sessions) progressed over the course of a programme, a weighted mean was calculated. Further details of data extraction can be found in supplementary methods.

A number of variations of HISI exist, including the statistical inverse (the hepatic insulin resistance index; HIRI). Studies reporting these alternatives were included in qualitative review but were only included in quantitative meta-analysis when raw data were available for the calculation of HISI as originally described (24):

$$1000 / (\text{EGP } [\text{mg} \bullet \text{m}^{-2} \bullet \text{min}^{-1}] \text{ x fasted plasma insulin } [\mu\text{U} \bullet \text{mL}^{-1}])$$

Studies that reported EGP and fasted plasma insulin (FPI) separately were also considered, but were excluded from all analyses unless raw data were available for the calculation of HISI as above. Mean values of EGP and FPI were not combined. Similarly, when study design allowed the calculation of $\%EGP_{supp}$ but it was not reported, raw data were requested.

Risk of bias assessment

Studies were assessed for risk of bias using a modified Downs and Black scale (30). This checklist includes 26 items divided into categories of (i) reporting, (ii) external validity, (iii) internal validity – bias, (iv) internal validity – confounding and (v) power. Modifications made to the original scale are outlined in supplementary methods. Consensus between the two independent assessors (JS/JK) was ensured. Publication bias was assessed using funnel plots.

Meta-analyses

Pooled characteristics of study participants are presented as weighted means, accounting for differences in sample size, along with the range. Quantitative analysis was conducted using commercially available software (Stata IC, Version 14.1, StataCorp LP, Texas, USA). Pooled mean differences with 95% confidence intervals (95% CI) were calculated for primary outcomes using random effects models and heterogeneity was assessed quantitatively using the I^2 statistic.

Where possible, primary outcomes were analysed in two ways:

Within-group analysis: The change from pre- to post-intervention measurements in all exercise groups of all eligible studies.

Between-group analysis: The difference in the change from pre- to post-intervention between exercise and control groups in RCTs only.

In RCTs with multiple exercise groups, groups were combined as outlined in supplementary methods. When groups were not suitable to be combined (for example, aerobic and resistance exercise training groups), data from the aerobic intervention group was used.

Subgroup analyses and meta-regression

Subgroup analyses were performed to investigate whether the presence of significant weight loss (defined as a statistically significant reduction in body weight from pre- to post-intervention) explained heterogeneity in the response of IHTG to exercise training. The influence of the exercise mode (aerobic, high-intensity interval (HIIT), resistance or combined aerobic/HIIT-plus-resistance training) was also investigated, as was the exercise intensity (moderate- or high-intensity) of aerobic and HIIT interventions. Exercise intensity was categorised according to published criteria (31), which are summarised in Table 1. One

study (32) prescribed exercise relative to maximal workload. This study was categorised using the same percentage categories as those of $\dot{V}O_2$ peak. Meta-regression was also performed to explore the effects of intervention duration and the magnitude of body weight change on changes in IHTG. All subgroup analyses and meta-regressions were performed using the mean change from pre- to post-training in all exercise groups of eligible studies. Secondary analyses of hepatic insulin sensitivity were not performed due to the limited number of studies identified.

Results

Literature search

Figure 1 presents a flowchart of the literature search and study selection processes. To summarise, 20,055 records were returned by the six online databases, along with five from reference lists of eligible manuscripts. Of these, 111 manuscripts underwent full assessment and 21 were eligible for inclusion (20 for meta-analyses). Twenty were complete articles and one was a conference abstract, although the latter has since been published in full (33). Table 2 presents an overview of eligible studies, but readers are directed to supplementary materials (Tables S1 to S3) for more detailed description.

Insert Figure 1 here

Risk of bias assessment

Full results of the risk of bias assessment can be found in supplementary materials (Table S4). Studies scored highly on items related to *reporting*, with the exception of reporting adverse events, and *internal validity*. Seven studies (11,18,34–38) blinded the investigators performing assessments of IHTG, but allocation concealment was only performed in three out of 10 RCTs (34,37,38). Conversely, studies scored poorly in relation to *external validity*, primarily due to an inability to determine whether recruited participants were representative of the entire population or of those who were approached to participate. Funnel plots suggested minimal evidence of publication bias (Figure S1), although the plot of all intervention groups investigating IHTG suggested a small bias towards studies reporting small effects. This would, if anything, result in an attenuated pooled effect. Seven studies recorded energy intake using self-reported food diaries (11,35,39–42) or a validated food frequency questionnaire (37). All of these reported no change in energy intake from pre- to

post-intervention, although one (41) reported a small increase in carbohydrate intake in participants completing a high-intensity, low-volume exercise programme. One study (43) prescribed a weight maintenance diet to participants. A further 10 studies instructed participants to maintain their dietary habits throughout the duration of study involvement without formally monitoring diet (18,33,34,38,44–49), whilst three manuscripts make no reference to the control of dietary intake (12,32,36).

The effects of exercise training on IHTG

Eighteen studies reported the effects of exercise training on IHTG (11,12,18,33–37,39–42,44–48) (Table 2). Only one of these used paired liver biopsy (18), reporting no significant effect of 6-months resistance exercise on the percentage of hepatocytes affected by steatosis in individuals with NAFLD. The remaining 17 studies used ^{1}H-MRS to measure IHTG so, to reduce heterogeneity, only these studies were included in subsequent meta-analyses. These studies contained 19 exercise groups and a combined total of 373 participants (male: 151 [40.5%]; female: 182 [48.8%]; data not reported: 40 [10.7%]). Participants had a weighted mean age of 50 [range 15.5 to 60] years and were overweight or obese (body mass index: 30.6 [27.8 to 37.1] kg•m^{-2}; body fat percentage: 35.6 [28.7 to 43.7] %; waist circumference: 101.2 [95.2 to 111.9] cm). Participants were reported as sedentary and/or inactive and had low aerobic capacity (peak oxygen uptake: 25.2 [21.8 to 38.7] ml•kg^{-1}•min^{-1}). Two studies actively recruited individuals with T2DM (34) or dysregulated glucose metabolism (37), whilst the mean baseline characteristics of seven other studies (11,36,38,39,46–48) met diagnostic criteria for impaired fasted glucose (weighted mean fasted glucose: 5.61 [4.09 to 6.80] mmol•L^{-1}) (50). The weighted mean IHTG at baseline was 15.8 [6.9 to 23.1] %.

Interventions included aerobic (n = 11), HIIT (n = 3), resistance (n = 2), combined aerobic/HIIT-plus-resistance (n = 2) and acceleration/vibration (n = 1) exercise training, ranging from seven days to 24 weeks (mode: 12 weeks). Session frequency ranged from two to seven times per week (mode: three times per week) for 30 to 60 minutes. Six aerobic interventions used moderate-intensity exercise whilst the remaining five, along with all of the HIIT interventions, were categorised as high-intensity.

Ten of the included studies were RCTs, containing a combined 283 and 169 participants in exercise and control groups, respectively (Table 2). Pooled participant and intervention characteristics of RCTs only can be found in supplementary materials (Tables S5 and S6). There were no significant differences between the pooled characteristics of RCTs and those of all eligible studies ($P \geq 0.13$). Participants in RCT control groups were instructed to maintain standard care (n = 5) or habitual lifestyle activities (n = 1), prescribed a low-intensity stretching programme (n = 2) or attended sessions providing education on the health benefits of exercise (n = 2).

Fourteen of the 17 studies reported a statistically significant benefit of exercise on IHTG either within-group (33,37,40,42,44), between-group (11,12), or both (34–36,38,41,47,48). In the two studies with multiple exercise groups, exercise elicited a significant reduction in both groups (38,41). One RCT reported a significant reduction from baseline, but this was not significant when compared to the change in the control group (40). Of the three studies that reported no benefit of exercise, two were short interventions (performing exercise on seven consecutive days) (39,46), whilst the other was a resistance exercise programme in obese adolescents (45).

When data from pre- to post-exercise in all interventions were pooled, a statistically significant benefit of exercise training was found (Figure 2), but high heterogeneity was also apparent. In a sensitivity analysis of RCTs only, the significant benefit of exercise was strengthened (mean difference in change between groups [95% CI]: -3.61 [-4.68 to -2.54] %; Figure S2), and results were highly homogeneous (I^2 < 0.1%, P = 0.84). Therefore, to allow the inclusion of maximum data, subgroup analyses and meta-regressions were performed using the within-group change in all interventions.

Insert Figure 2 here

Exercise training significantly reduced IHTG in the absence of weight loss. However, when significant weight loss occurred, the pooled effect was substantially greater (Figure 3). Furthermore, meta-regression displayed a significant positive relationship between the change in body weight (relative to baseline) and the absolute change in IHTG (β = 0.99 [95% CI: 0.62 to 1.36], P < 0.001; Figure S3). A significant relationship was also apparent between intervention duration and change in IHTG (β = -0.27 [95% CI: -0.35 to -0.19], P < 0.001; Figure S4), suggesting that as the duration of intervention increases, so does the magnitude of reduction in IHTG. The duration of interventions that elicited significant weight loss versus those that did not were similar (median [range]: 12 [8 to 24] vs. 12 [1 to 16] weeks), but bivariate Pearson's correlation analysis showed a significant positive relationship between the duration of intervention and magnitude of weight loss elicited (r^2 = 36%, P < 0.01).

Insert Figure 3 here

Figure 2 displays the mean change from baseline in IHTG for all interventions categorised by exercise type. The pooled effect on IHTG for aerobic exercise interventions was greater than that for each other mode of exercise, as well as the pooled mean for all interventions. However, the high prevalence of aerobic interventions in comparison to other types of intervention should be noted. When interventions were grouped according to exercise intensity, the pooled effect for moderate-intensity interventions was greater than that of the high-intensity exercise programmes (-4.82 [-7.00 to -2.65] %, I^2 = 75.5%, P = 0.001 vs. (-2.89 [-4.25 to -1.53] %, I^2 = 73.2%, P < 0.001). The intervention duration of the moderate and high-intensity interventions were similar (median [range]: 14 [4 to 24] vs. 12 [1 to 24] weeks).

Overview of studies investigating the effects of exercise on hepatic insulin sensitivity

Eight studies, containing a total of 10 exercise groups, reported the effects of exercise training on hepatic insulin sensitivity (18,32,33,35,43,45,49,51) (Table 2). Four studies reported HISI (33,43–45), although three presented EGP (and thus HISI) in different units to those outlined above. Two studies reported HIRI (18,35). Four studies were able to provide raw data for the re-calculation of HISI (18,35,44,45), along with two that reported EGP and FPI separately (32,49). As such, seven studies (eight exercise groups) were included in meta-analysis of changes in HISI with exercise training. Only two of these (35,49) were RCTs with a non-intervention/standard care control group (containing a combined 22 and 14 participants in exercise and control groups, respectively) so only within-group analysis was conducted. Three studies also reported $\%EGP_{supp}$ with low-dose insulin infusion (33,35,49) but, due to this limited number, meta-analysis was not performed. Seven further studies were found that utilised a study design allowing the calculation of at least one of HISI or $\%EGP_{supp}$, but

neither were reported (52–58). Whilst the authors of five of these studies kindly replied to requests for raw data, none were able to provide it.

The effects of exercise training on basal hepatic insulin sensitivity

The study that was excluded from meta-analysis of changes in HISI reported a tendency for a reduction in HIRI in obese adolescent girls following 12 weeks of resistance exercise training, but not after 12 weeks of moderate- to high-intensity aerobic exercise (43). The remaining eight exercise groups were pooled and had a combined total of 105 participants (male: 84 (80%); female: 20 (19%); data not available: 1 (1%)). Participants had a weighted mean age of 43 [range 15.5 to 59] years and, as per study selection criteria, were overweight or obese (body mass index: 31.3 [27.6 to 35.3] $kg•m^{-2}$; body fat percentage: 34.0 [25.5 to 40.8] %). Participants were reported as sedentary and/or inactive and had low aerobic capacity (maximal or peak oxygen uptake: 24.7 [21.6 to 32.0] $ml•kg^{-1}•min^{-1}$). Five studies (five exercise groups) were conducted in individuals with diagnosed NAFLD or in those with baseline characteristics that met diagnostic criteria as outlined above (18,33,35,45,51). One study included separate groups of patients with impaired fasted glucose and T2DM (32) but, according to mean baseline characteristics, all other studies recruited individuals with normal fasted glycaemia (weighted mean fasted glucose for all studies was 5.36 [4.70 to 9.00] $mmol•L^{-1}$) (50). The weighted mean HISI at baseline was 0.99 [0.58 to 2.09] $mg•m^{-2}•min^{-1}$ per $\mu U•mL^{-1}$.

Studies included aerobic (n = 3), HIIT (n = 1), resistance (n = 2) and combined (n = 2) exercise interventions for six (n = 2), 12 (n = 5) or 24 (n = 1) weeks. Participants exercised on two to four days per week with sessions ranging from 20 to 60 minutes. One aerobic intervention, and the aerobic component of the combined exercise programmes, utilised

moderate-intensity exercise, whilst the remaining aerobic interventions and the HIIT intervention were categorised as high-intensity.

Two of the eight exercise groups displayed a statistically significant improvement in HISI with exercise, both of which were in adolescents (45,51). One study reported a tendency for reduced HIRI after exercise training, but this effect was statistically significant when HISI was re-calculated as above. Neither RCT reported a significant difference between exercise and control groups (35,49). However, when data were pooled, a statistically significant benefit of exercise was found (Figure 4). Based on the weighted mean HISI at baseline, this pooled effect represents a relative improvement of approximately 13%. Two studies in obese adolescents reported a reduction in basal EGP after aerobic or resistance exercise training (45,51), but EGP was unaffected in all other studies. In contrast, FPI was significantly reduced in five of the exercise groups (32,33,35,51), whilst the mean reduction in another (18) approached statistical significance. One study (35) reported a statistically significant reduction in body weight from pre- to post-exercise training (2.5%) but this was not associated with an improvement in HISI. Another study (18) reported a mean reduction in body weight of similar magnitude (2.6%) which, although not statistically significant, was associated with a significant improvement in HISI.

Insert Figure 4 here

The effects of exercise training on insulin-stimulated hepatic insulin sensitivity

Participant and intervention characteristics for the three studies examining the effects of exercise on $\%EGP_{supp}$ can be found in supplementary materials (Tables S2 and S3). The two RCTs that reported HISI also reported $\%EGP_{supp}$. One RCT reported a significant

improvement in $\%EGP_{supp}$, compared to the control group, after six weeks of aerobic exercise training, despite no change in total body weight or IHTG (49). In contrast, $\%EGP_{supp}$ was reportedly unaffected by either twelve weeks of aerobic training (35) or six weeks of HIIT (33).

Discussion

The prominent findings of this review are that structured exercise training, independent of dietary intervention, reduces IHTG in individuals with NAFLD. Importantly, whilst this effect is apparent without weight loss, the magnitude of reduction increases in direct proportion to the amount of weight loss induced by the intervention. Furthermore, our analyses indicate that exercise training for six to 24 weeks may also improve basal hepatic insulin sensitivity by approximately 13%.

Previous reviews report that exercise training significantly reduces IHTG with a moderate to large pooled effect size (13,15,17). The restriction of the current meta-analysis to a single technique (^{1}H-MRS) allowed us to report this pooled effect as the absolute mean difference and our findings suggest that exercise training for between one and 24 weeks (mode 12 weeks) elicits an absolute reduction in IHTG of approximately 2.2 to 4.7% (mean ~3.5%); re-enforcing the meaningful therapeutic role of exercise for individuals with NAFLD. An important finding to emerge from this meta-analysis is the impact of weight loss as a mediator of the reduction in IHTG associated with exercise training interventions. This outcome is consistent with previous reviews (59,60), which have highlighted the more potent impact of weight loss *per se* (primarily through dietary energy restriction) than the independent effect of exercise in the absence of body weight reduction. Specifically, our data show that whilst IHTG is significantly reduced in the absence of exercise-induced weight loss, the magnitude of effect is more than two-fold greater when weight loss occurs (-2.16 vs. -4.87%). Meta-regression suggests that each 1% relative reduction in body weight is associated with approximately 1% absolute reduction in IHTG. Interestingly, an almost identical relationship can be seen in studies that have examined IHTG responses to short-, medium- and long-term dietary energy restriction interventions (61–63). These data therefore

illustrate that relative changes in IHTG are several-fold greater than associated alterations in body weight regardless of physiological stimulus. This overriding influence of weight loss may also explain why previous reviews have not found additive benefits of exercise when combined with dietary intervention (13,14). In these scenarios, large energy deficits created by dietary modification may dilute the much smaller contribution of exercise (64). Consequently, whilst exercise alone may be effective at reducing IHTG, the greatest therapeutic benefits will be realised when exercise interventions contribute to weight loss in combination with dietary energy restriction.

These findings have direct implications for exercise prescription in NAFLD. Specifically, the greatest impact of exercise training on IHTG is likely to occur with exercise that is associated with the greatest weight loss (14). Evidence suggests that aerobic exercise interventions typically evoke a higher amount of weight loss than anaerobic exercise modalities (65). The superiority of aerobic exercise interventions for reducing IHTG in individuals with NAFLD is supported by the present results and those of a previous meta-analysis (15). Consequently, although resistance exercise training and HIIT promote a reduction in IHTG in patients with NAFLD, greater benefits will likely be achieved through continuous aerobic exercise protocols such as running, swimming and cycling.

Exercise volume may also be an important variable which helps to explain why our analyses documented a larger reduction in IHTG with moderate- compared to high-intensity exercise interventions. Specifically, compared with shorter intense bouts of exercise, continuous moderate-intensity protocols commonly exhibit a greater total exercise volume and, consequently, energy expenditure. This higher level of energy expenditure may elicit a greater impact on metabolism, energy balance and IHTG. It is, however, important to

consider that exercise-related energy expenditure may not necessarily translate into greater total daily energy expenditure (66,67). Furthermore, given the inability to accurately calculate exercise-related energy expenditure in our review, further research is needed to investigate the precise relationship between exercise-related energy expenditure and IHTG.

Our analyses also demonstrate a significant relationship between the duration of exercise interventions and the change in IHTG, and a positive relationship between the duration of exercise training and the magnitude of weight loss. Each week of exercise training is associated with a reduction in IHTG of approximately 0.27%. Collectively, our findings highlight the importance of developing sustainable exercise interventions, which, in combination with dietary strategies, may elicit the greatest benefits on IHTG in individuals with NAFLD.

The second part of this review examined the influence of exercise training on hepatic insulin sensitivity. Hepatic insulin resistance, which is strongly correlated with elevated IHTG (3,7,8), contributes to impaired glycaemic control in the pathogenesis of T2DM (6,9,10). We assessed the impact of exercise interventions on HISI and $\%EGP_{supp}$, which are measures of hepatic insulin sensitivity in the basal and insulin-stimulated states, respectively. The paucity of studies examining these effects meant that our analyses were conducted using any study that recruited individuals with overweight or obesity, who are thus at increased risk of NAFLD, in addition to studies exclusively in patients with NAFLD.

In total, we identified eight studies (two of which had two exercise groups) which assessed the impact of exercise on basal hepatic insulin sensitivity (18,32,33,35,43,45,49,51). Seven studies had sufficient data for inclusion in our meta-analysis but only two of which were

RCTs. Therefore, our analysis was restricted to within-group changes in eight exercise groups. Interestingly, despite only three exercise groups displaying significant improvements in HISI from pre- to post- intervention (18,45,51), our pooled analysis identified a statistically significant increase of approximately 13%. In adults, basal rates of EGP were unaffected by exercise, but this improvement in basal hepatic insulin sensitivity may be reflected by a reduction of FPI. The clinical relevance of this magnitude of improvement in basal hepatic insulin sensitivity for individuals that are overweight and obese is not immediately clear. However, this novel finding suggests that exercise training favourably modifies this important parameter in individuals at risk of NAFLD and T2DM.

Three studies reported the effects of exercise on $\%EGP_{supp}$ (33,35,49), two of which were RCTs employing aerobic exercise interventions of six and 12 weeks (35,49). While one study reported significant improvement in $\%EGP_{supp}$, no change was reported in the other. Therefore, we cannot draw firm conclusions on the impact of exercise training on insulin-stimulated hepatic insulin sensitivity at this time.

It is notable that we identified a further seven studies whose methods permitted the calculation of HISI or $\%EGP_{supp}$ but data weren't presented or available. Furthermore, when hepatic insulin sensitivity was reported, the precise details of the experimental methods employed, units used for presentation of outcomes and calculation of indices of hepatic insulin sensitivity, varied between studies. This review, therefore, highlights the need for greater methodological and reporting consistency when assessing hepatic insulin resistance (e.g. standardisation of low-dose insulin infusion when undertaking dual-stepped hyperinsulinaemic-euglycaemic clamps and consistent use of units).

Our meta-analysis of the effects of exercise training on IHTG in individuals with NAFLD, and the mediating influence of weight loss, is the most precise quantitative synthesis to date. Furthermore, this is the first systematic review and meta-analysis assessing the impact of exercise interventions on hepatic insulin sensitivity. However, a few important considerations are noteworthy. A range of exercise interventions are identified and our analyses of the effects of exercise on IHTG display significant heterogeneity. Whilst we explore potential sources of this heterogeneity, it is assumed that these studies are suitable for data pooling. Secondly, although most included studies attempt to control habitual diet, this is notoriously difficult (68) and the potential for dietary changes to influence study outcomes must, therefore, be recognised. Additionally, our subgroup analyses investigating the influence of weight loss on IHTG were performed with studies categorised according to statistical, rather than clinical, significance. This has the potential to exclude studies from the weight loss group that demonstrate physiologically relevant, but not statistically significant, weight loss. Notably, however, this is unlikely in our analyses because, in the 'no weight loss' studies, the largest mean relative reduction in body weight after exercise training was 1.2%. Furthermore, it assumed that weight loss resulting from exercise training is primarily reflective of a reduction in fat mass but some exercise regimens may promote the synthesis of skeletal muscle; attenuating any reduction in total body weight. It should also be noted that while a reduction in IHTG may be indicative of improved metabolic heath, these may be mediated by a reduction in hepatic lipid intermediates rather that IHTG *per se* (3–5). Finally, the limited number of studies investigating hepatic insulin sensitivity means that our findings should be taken with caution. Large RCTs are required to further investigate the effects of exercise training on hepatic insulin sensitivity, particularly in individuals with NAFLD and T2DM.

In conclusion, this systematic review and meta-analysis has shown that exercise training reduces IHTG in individuals with NAFLD and, whilst benefits can be realised in the absence of weight loss, reductions in IHTG are proportionally related to the magnitude of weight loss induced. Furthermore, exercise training may improve basal hepatic insulin sensitivity in individuals that are overweight or obese, which may have beneficial implications for the management of NAFLD and T2DM.

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Table 1 – Categories of exercise intensity

	RPE	**%HR max**	**%HRR**	**%$\dot{V}O_2$ peak**
Moderate-intensity	12 – 13	64 – 76	40 – 59	46 – 63
High-intensity	14 – 17	77 – 95	60 – 89	64 – 90

Table 2 - Overview of included studies

First Author (Year of Publication)	Study Design	Sample Size (M/F)	Exercise Mode	Intervention Duration	Session Frequency	Exercise Intensity (Category)	Technique used for Assessment of IHTG	Index of Basal Hepatic IS Originally Reported	Details of Low-Dose Insulin Infusion	Weight Change with Exercise Training (mean % change from baseline)
Cassidy (2016)	RCT	Ex: 12 (10/2) Con: 11 (8/3)	HIIT	12 weeks	3 times per week	High	^{1}H-MRS	-	-	-1.1 $^{\beta}$
Cuthbertson (2016)	RCT	Ex: 30 (23/7) [12 (8/3/1 NR)] Con: 20 (16/4) [7 (3/4)]	Aerobic	12 weeks	3 – 5 times per week	Moderate	^{1}H-MRS	HIRI	0.3 mU•kg^{-1}•min^{-1} for 120 min	-2.5 $^{\alpha, \beta}$
Hallsworth (2011)	RCT	Ex: 11 (NR) Con: 8 (NR)	Resistance	8 weeks	3 times per week	N/A	^{1}H-MRS	-	-	0.0
Hallsworth (2015)	RCT	Ex: 12 (6/6) Con: 11 (10/1)	HIIT	12 weeks	3 times per week	High	^{1}H-MRS	-	-	-1.6 $^{\alpha, \beta}$
Haus (2013)	Uncontrolled Intervention	Ex: 17 (NR)	Aerobic	1 week	7 times per week	High	^{1}H-MRS	-	-	0.2
Hickman (2013)	RCT*	Ex: 9 (7/2) [13 (9/4)]	Resistance	24 weeks	3 times per week	N/A	Biopsy†	HIRI	-	-2.6
Houghton (2017)	RCT	Ex: 12 (7/5) Con: 12 (7/5)	Combined (HIIT + Resistance)	12 weeks	3 times per week	High	^{1}H-MRS	-	-	1.1

Johnson (2009)	RCT	Ex: 12 (NR) Con: 7 (NR)	Aerobic	4 weeks	3 times per week	Moderate	^{1}H-MRS	-	-	-0.3
Keating (2015)	RCT	Ex1: 12 (6/6) Ex2: 11 (5/6) Con: 12 (3/9)	Aerobic	8 weeks	Ex1: 3 sessions per week Ex2: 4 sessions per week	Ex1: High Ex2: Moderate	^{1}H-MRS	-	-	Ex1: -1.2 $^{\alpha, \beta}$ Ex2: -1.5 $^{\alpha, \beta}$
Langleite (2016)	Uncontrolled Intervention	Ex: 11 (11/0)	Combined (Aerobic + HIIT + Resistance)	12 weeks	4 times per week (1 aerobic, 1 HIIT, 2 resistance)	High	^{1}H-MRS	-	-	-1.2
Lee (2013)	RCT	Ex1: [16 (0/16)] Ex2: [16 (0/16)] Con: [12 (0/12)]	Ex1: Aerobic Ex2: Resistance	12 weeks	3 times per week	High	-	HISI†	-	Ex1: -1.3 Ex2: -0.3
Malin (2013)	Uncontrolled Intervention	Ex: 13 (6/7)	Aerobic	1 week	7 times per week	High	^{1}H-MRS	-	-	0.6
Meex (2010)	Uncontrolled Intervention	Ex1: [20 (20/0)] Ex2: [17 (17/0)]	Combined (Aerobic + Resistance)	12 weeks	3 times per week (2 aerobic, 1 resistance)	Moderate	-	HISI$^{\#}$	-	Ex1: -1.1 Ex2: -1.0
Oh (2014)	Uncontrolled Intervention	Ex: 18 (4/14)	Vibration / Acceleration	6 weeks	3 times per week	N/A	^{1}H-MRS	-	-	-0.4 $^{\alpha}$
Pugh (2014)	RCT	Ex: 13 (7/6) Con: 8 (4/4)	Aerobic	16 weeks	3 – 5 times per week	Moderate	^{1}H-MRS	-	-	-2.4
Sargeant (2018)	Controlled Longitudinal Intervention	Ex: 9 (9/0) [8 (8/0)]	HIIT	6 weeks	3 times per week	High	^{1}H-MRS	HISI	20 mU•m^{-2}•min^{-1} for 120 min	-1.2

Shojaee-Moradie (2007)	RCT	Ex: [10 (10/0)] Con: [7 (7/0)]	Aerobic	6 weeks	3 times per week	High	-	HISI[#]	0.3 mU•kg^{-1}•min^{-1} for 120 min	-0.8
Sullivan (2012)	RCT	Ex: 12 (4/8) Con: 6 (1/5)	Aerobic	16 weeks	5 times per week	Moderate	^{1}H-MRS	-	-	-0.2 [α]
van der Heijden (2010a)[‡]	Uncontrolled Intervention	Ex: 15 (7/8) [15 (7/8)]	Aerobic	12 weeks	4 times per week	High	^{1}H-MRS	HISI	-	-0.5
van der Heijden (2010b)	Uncontrolled Intervention	Ex: 7 (NR) [12 (6/6)]	Resistance	12 weeks	2 times per week	N/A	^{1}H-MRS	HISI	-	2.6 [α]
Zhang (2016)	RCT	Ex1: 73 (22/51) Ex2: 73 (21/52) Con: 74 (28/46)	Aerobic	24 weeks	5 times per week	Ex1: Moderate Ex2: High	^{1}H-MRS	-	-	Ex1: -2.8 [α, β] Ex2: -6.0 [α β]

Table & Figure Legends

Table 1 – Categories of exercise intensity. Adapted from (31); **%**HR max: percentage of maximal heart rate; %HRR: percentage of heart rate reserve; %$\dot{V}O_2$ peak: percentage of peak oxygen uptake; RPE: rating of perceived exertion (69).

Table 2 – Overview of included studies. Sample sizes in squared brackets represent the number of participants included in hepatic insulin sensitivity outcomes; Mean changes in body weight with exercise are as reported in the original manuscript ($^{\alpha}$ indicates significantly different from baseline, $^{\beta}$ indicates significantly different from non-exercise control group); Exercise intensity is categorised according to published criteria (31), which are summarised in Table 1; *Study did not include a 'standard care' or 'no intervention' group, exercise was compared with hypocaloric diet; †Study was excluded from one or more meta-analyses - Hickman et al (2013) was removed from meta-analyses of changes in hepatic steatosis to reduce heterogeneity as it was the only study using liver biopsy to assess IHTG. Lee et al (2013) was removed from meta-analysis of changes in basal hepatic insulin sensitivity because raw data were not available to allow re-calculation of HISI as outlined by Matsuda and DeFronzo (1999); $^{\#}$Published manuscript contained no index of hepatic insulin sensitivity. HISI was calculated after authors provided raw data; ‡Manuscript refers to the same study as van der Heijden et al (2009); ^{1}H-MRS: Proton magnetic resonance spectroscopy; Con: Control group; Ex1/2: Exercise group 1/2; HISI: hepatic insulin sensitivity index; IHTG: intrahepatic triglyceride; N/A: not applicable; NR: not reported; RCT: randomised controlled trial; %EGP_{supp}: percentage suppression of endogenous glucose production by low-dose insulin infusion.

Figure 1 – Flowchart of literature search process. An overview of the literature search and study selection process.

Figure 2 – Meta-analysis of the pooled effect of exercise training on IHTG from pre- to post-training in all exercise groups of all eligible studies. Studies are grouped by exercise mode. IHTG: intrahepatic triglyceride; 95% CI: 95% confidence interval; HIIT: high-intensity interval training; Combined: combined aerobic- or HIIT-plus-resistance exercise training.

Figure 3 – Meta-analysis of the pooled effect of exercise training on IHTG from pre- to post-training in all exercise groups of all eligible studies when studies are grouped into those that elicited weight loss versus those that did not. IHTG: intrahepatic triglyceride; 95% CI: 95% confidence interval.

Figure 4 – Meta-analysis of the pooled effect of exercise training on HISI from pre- to post-training in all exercise groups of all eligible studies. HISI: hepatic insulin sensitivity index; 95% CI: 95% confidence interval; Combined: combined aerobic-plus-resistance exercise training; HIIT: high-intensity interval training.

Figure 1

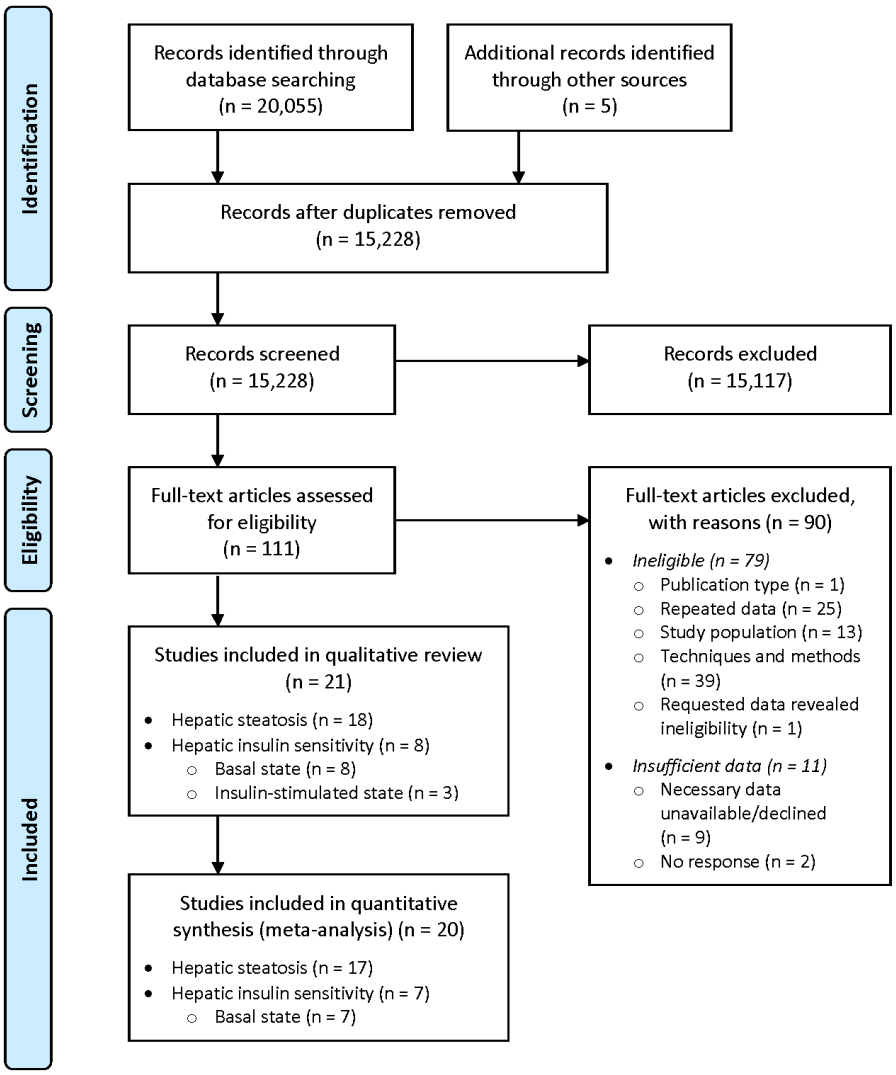

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 20,055)
Additional records identified through other sources (n = 5)
Records after duplicates removed (n = 15,228)
Records screened (n = 15,228)
Records excluded (n = 15,117)
Full-text articles assessed for eligibility (n = 111)
Full-text articles excluded, with reasons (n = 90)
Ineligible (n = 79)
Publication type (n = 1)
Repeated data (n = 25)
Study population (n = 13)
Techniques and methods (n = 39)
Requested data revealed ineligibility (n = 1)
Insufficient data (n = 11)
Necessary data unavailable/declined (n = 9)
No response (n = 2)
Studies included in qualitative review (n = 21)
Hepatic steatosis (n = 18)
Hepatic insulin sensitivity (n = 8)
Basal state (n = 8)
Insulin-stimulated state (n = 3)
Studies included in quantitative synthesis (meta-analysis) (n = 20)
Hepatic steatosis (n = 17)
Hepatic insulin sensitivity (n = 7)
Basal state (n = 7)

Figure 2

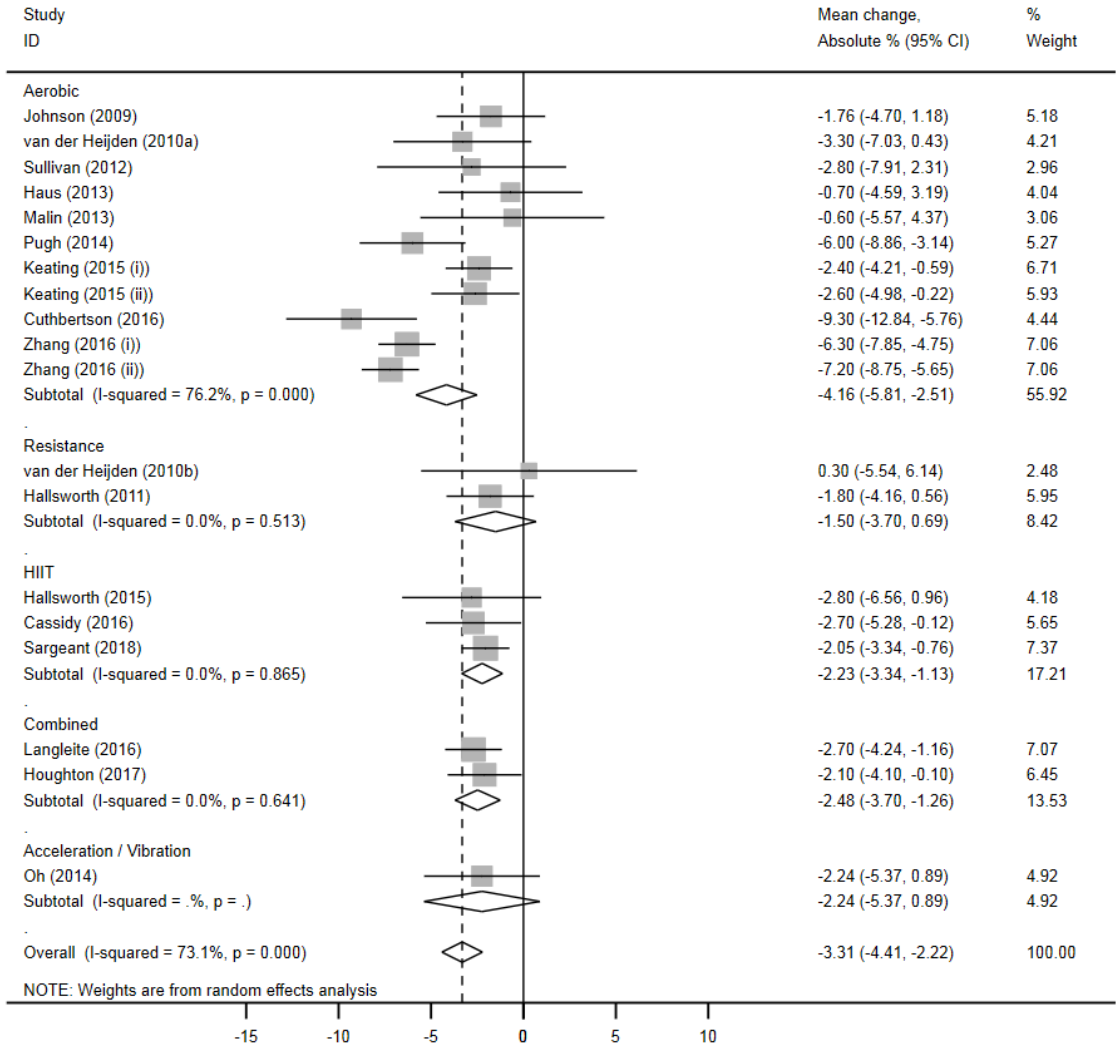

Study
ID
Mean change,
Absolute % (95% CI)
%
Weight
Aerobic
Johnson (2009) -1.76 (-4.70, 1.18) 5.18
van der Heijden (2010a) -3.30 (-7.03, 0.43) 4.21
Sullivan (2012) -2.80 (-7.91, 2.31) 2.96
Haus (2013) -0.70 (-4.59, 3.19) 4.04
Malin (2013) -0.60 (-5.57, 4.37) 3.06
Pugh (2014) -6.00 (-8.86, -3.14) 5.27
Keating (2015 (i)) -2.40 (-4.21, -0.59) 6.71
Keating (2015 (ii)) -2.60 (-4.98, -0.22) 5.93
Cuthbertson (2016) -9.30 (-12.84, -5.76) 4.44
Zhang (2016 (i)) -6.30 (-7.85, -4.75) 7.06
Zhang (2016 (ii)) -7.20 (-8.75, -5.65) 7.06
Subtotal (I-squared = 76.2%, p = 0.000) -4.16 (-5.81, -2.51) 55.92
Resistance
van der Heijden (2010b) 0.30 (-5.54, 6.14) 2.48
Hallsworth (2011) -1.80 (-4.16, 0.56) 5.95
Subtotal (I-squared = 0.0%, p = 0.513) -1.50 (-3.70, 0.69) 8.42
HIIT
Hallsworth (2015) -2.80 (-6.56, 0.96) 4.18
Cassidy (2016) -2.70 (-5.28, -0.12) 5.65
Sargeant (2018) -2.05 (-3.34, -0.76) 7.37
Subtotal (I-squared = 0.0%, p = 0.865) -2.23 (-3.34, -1.13) 17.21
Combined
Langleite (2016) -2.70 (-4.24, -1.16) 7.07
Houghton (2017) -2.10 (-4.10, -0.10) 6.45
Subtotal (I-squared = 0.0%, p = 0.641) -2.48 (-3.70, -1.26) 13.53
Acceleration / Vibration
Oh (2014) -2.24 (-5.37, 0.89) 4.92
Subtotal (I-squared = .%, p = .) -2.24 (-5.37, 0.89) 4.92
Overall (I-squared = 73.1%, p = 0.000) -3.31 (-4.41, -2.22) 100.00
NOTE: Weights are from random effects analysis
-15
-10
-5
0
5
10

Figure 3

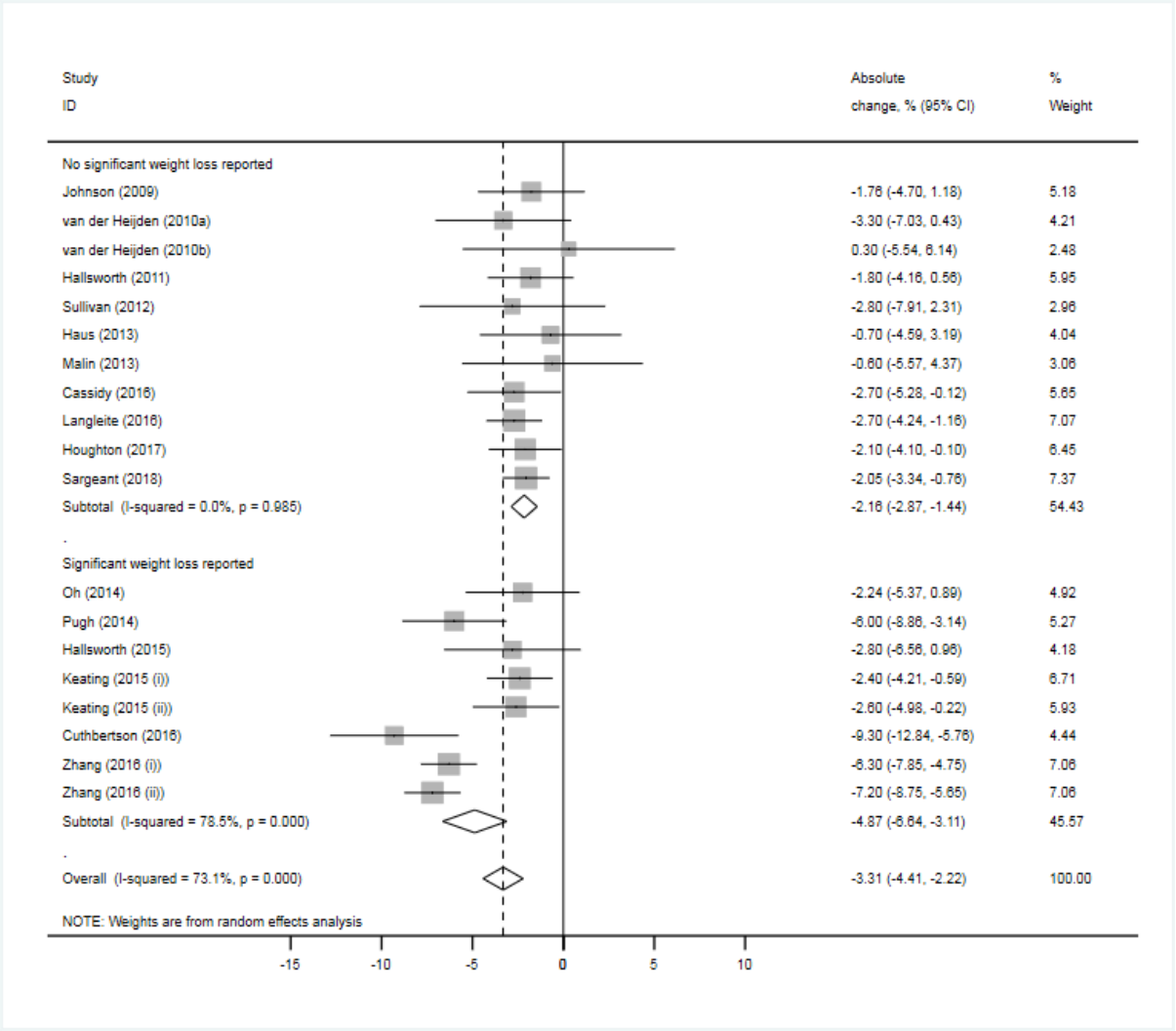
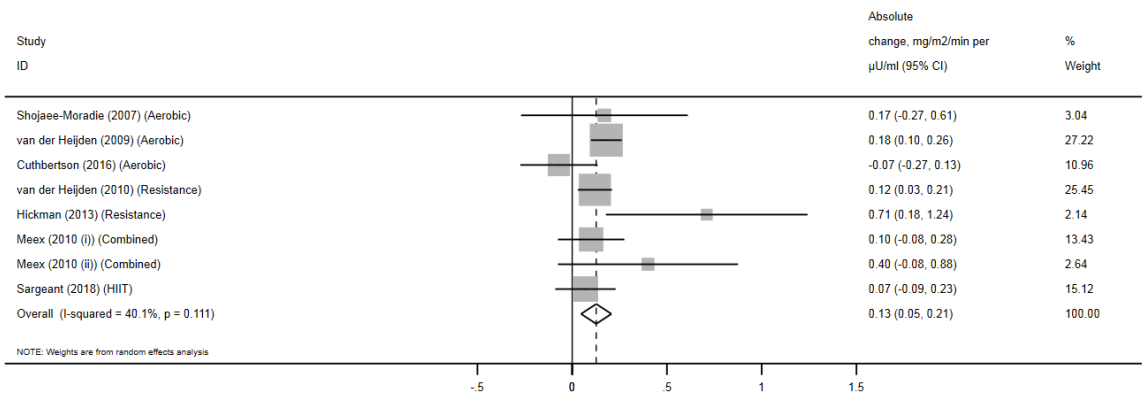

Study
ID
Absolute
change, % (95% CI)
%
Weight
No significant weight loss reported
Johnson (2009)
-1.76 (-4.70, 1.18)
5.18
van der Heijden (2010a)
-3.30 (-7.03, 0.43)
4.21
van der Heijden (2010b)
0.30 (-5.54, 6.14)
2.48
Hallsworth (2011)
-1.80 (-4.16, 0.56)
5.95
Sullivan (2012)
-2.80 (-7.91, 2.31)
2.96
Haus (2013)
-0.70 (-4.59, 3.19)
4.04
Malin (2013)
-0.60 (-5.57, 4.37)
3.06
Cassidy (2016)
-2.70 (-5.28, -0.12)
5.65
Langleite (2016)
-2.70 (-4.24, -1.16)
7.07
Houghton (2017)
-2.10 (-4.10, -0.10)
6.45
Sargeant (2018)
-2.05 (-3.34, -0.76)
7.37
Subtotal (I-squared = 0.0%, p = 0.985)
-2.16 (-2.87, -1.44)
54.43
.
Significant weight loss reported
Oh (2014)
-2.24 (-5.37, 0.89)
4.92
Pugh (2014)
-6.00 (-8.86, -3.14)
5.27
Hallsworth (2015)
-2.80 (-6.56, 0.96)
4.18
Keating (2015 (i))
-2.40 (-4.21, -0.59)
6.71
Keating (2015 (ii))
-2.60 (-4.98, -0.22)
5.93
Cuthbertson (2016)
-9.30 (-12.84, -5.76)
4.44
Zhang (2016 (i))
-6.30 (-7.85, -4.75)
7.06
Zhang (2016 (ii))
-7.20 (-8.75, -5.65)
7.06
Subtotal (I-squared = 78.5%, p = 0.000)
-4.87 (-6.64, -3.11)
45.57
.
Overall (I-squared = 73.1%, p = 0.000)
-3.31 (-4.41, -2.22)
100.00
NOTE: Weights are from random effects analysis
-15
-10
-5
0
5
10

Figure 4


Study
ID
Absolute
change, mg/m2/min per
µU/ml (95% CI)
%
Weight
Shojaee-Moradie (2007) (Aerobic)
0.17 (-0.27, 0.61)
3.04
van der Heijden (2009) (Aerobic)
0.18 (0.10, 0.26)
27.22
Cuthbertson (2016) (Aerobic)
-0.07 (-0.27, 0.13)
10.96
van der Heijden (2010) (Resistance)
0.12 (0.03, 0.21)
25.45
Hickman (2013) (Resistance)
0.71 (0.18, 1.24)
2.14
Meex (2010 (i)) (Combined)
0.10 (-0.08, 0.28)
13.43
Meex (2010 (ii)) (Combined)
0.40 (-0.08, 0.88)
2.64
Sargeant (2018) (HIIT)
0.07 (-0.09, 0.23)
15.12
Overall (I-squared = 40.1%, p = 0.111)
0.13 (0.05, 0.21)
100.00
NOTE: Weights are from random effects analysis
-.5
0
.5
1
1.5