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The acute effects of physical activity on cigarette cravings:

Systematic review and meta-analysis with individual participant data (IPD).

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Declaration of Interest

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ABSTRACT

Aims To conduct an updated systematic review and the first meta-analysis of experimental trials investigating the acute effects of short bouts of physical activity (PA) on Strength of Desire (SoD) and Desire to Smoke (DtS) using individual participant data (IPD). **Methods** A systematic review of literature and IPD meta-analyses included trials assessing the acute effects of short bouts of PA on SoD and DtS among temporarily abstaining smokers not using pharmaceutical aids for smoking cessation. Authors of eligible studies were contacted and raw IPD were obtained. Two-stage and one-stage IPD random effects meta-analyses were conducted. Participants engaging in PA were compared against control participants, using post-intervention SoD and DtS with baseline adjustments. **Results** A two-stage IPD meta-analysis assessing effects of PA on SoD yielded an average standardised mean difference (SMD) between PA and control conditions (across 15 primary studies) of -1.91 (95% CI: -2.59 to -1.22). A two-stage IPD meta-analysis assessing effects of PA on DtS yielded an average SMD between PA and control conditions (across 17 primary studies) of -2.03 (95% CI: -2.60 to -1.46). Additional meta-analyses, including those using a one-stage model, those including only parallel arm studies, and meta-analyses comparing only moderate exercise against a control condition, showed significant craving reduction following PA. Despite a high degree of between-study heterogeneity, effects sizes of all primary studies were in the same direction, with PA showing a greater reduction in cravings compared with controls. **Conclusions** There is strong evidence that physical activity acutely reduces cigarette craving.

Keywords: exercise, desire to smoke, smoking cessation aid

INTRODUCTION

In the UK, 21% of adults smoke, yet the majority of smokers (63%) want to give up smoking (1). Unaided quit attempts have only a 3-5% success rate after 6-12 months' abstinence, with most smokers relapsing within the first eight days (2). It has been well established that standard smoking cessation treatments, combining pharmacological and behavioural support are effective (3); nonetheless, success rates remain low, with less than 30% of people successfully quitting, even with the best available support (4-6). In addition, giving up smoking is associated with significant weight gain (7), and concern about weight gain is a possible reason for relapse, specifically among women (7). Also cravings during smoking cessation reliably predict relapse to smoking (8). Although physical activity (PA) is recommended as a smoking cessation aid (9), only limited evidence supports its effectiveness for aiding cessation (10), though there is some evidence to suggest that PA can help moderate weight gain following smoking cessation (7). A previous systematic review concluded that there is good evidence that PA acutely reduces cigarette cravings (10, 11); however, this phenomenon has not been quantified using the most rigorous statistical approach. Also, the growth of research (10) is indicative of a need to update the evidence on the acute effects of PA on cigarette cravings.

Results of individual and often small-scale studies may not be able to answer a research question definitively. Traditional meta-analysis methods involve combining and analysing aggregate data (usually obtained from a published study), and are an integral part of evidence based research (12). Individual participant data (IPD) meta-analysis has been described as the 'gold standard' method (13). Meta-analysis of IPD offers numerous advantages over the traditional approach to meta-analyses (i.e., using aggregated data from primary studies) and presents a reliable means of combining data from randomised controlled trials (RCTs) with the same outcome (14, 15, 16). The Cochrane Handbook for Systematic Reviews of Interventions suggests that IPD meta-analyses may be beneficial when many studies are either unpublished or published only in the 'grey literature' (i.e. unpublished literature, such as abstracts and working papers), when different analyses are applied to the results, and when

multivariate or other complex analyses are needed (17). IPD meta-analysis methods can minimise publication bias, improve data and analysis quality, and enhance interpretation of the findings, as well as support collaboration on future research (18). The issue of publication bias (and outcome reporting bias) is well acknowledged (19, 20); on average, published trials show a 9% larger intervention effect than grey literature trials (20). Including data from grey literature is a way of addressing this problem. Nevertheless, unpublished studies may also introduce bias into the review (17).

A recent study attempted to summarise the acute effects of PA on exercise and cigarette cravings, but they did not use individual participant data (IPD) and included only 10 studies in the meta-analyses (21). Although IPD meta-analysis is more time-consuming than aggregate meta-analysis (18), it offers advantages (12, 16); including enabling exploratory analyses such as heterogeneity examination and increases the power to detect any treatment effects across individuals in randomised trials. This study aimed to update the current evidence on the acute effects of PA on cigarette cravings, following a systematic review (11), and to collate IPD for use in quantifying the acute effects of PA on cigarette cravings.

METHODS

Search strategy

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conducting and reporting systematic reviews (22). A systematic review of literature was conducted, following the methodology described by Taylor *et al* (11). Online searches of electronic databases Sport Discus, MEDLINE, PubMed, Web of Science, EMBASE and PsycINFO were performed. Also, the Cochrane Tobacco Addiction Group specialised register, ETD Digital Library – Network Digital Library of Theses, and Dissertations and Proquest Digital Dissertations, were searched. Additionally, reference lists of relevant articles and annual meeting abstracts of the Society for Research on Nicotine and Tobacco (SRNT; published in 2007-2011) were hand searched. Requests for literature were posted on key list-serves (SALIS, OTRU-NET, SRNT, and Globalink),

and authors of published studies on exercise and smoking cessation interventions were contacted for any new literature. We restricted our search to articles written in English and published from 2004 onwards; the previous review (11), which we are updating, conducted searches until July 2006. Searches ended on 31st May 2011. The search terms were: “(smoking or smoking cessation) and (exercise or physical activity) and (craving\$ or withdrawal)”.

Inclusion/exclusion criteria

Eligible studies had to examine the acute effects of PA on either Desire to Smoke (DtS; 23) or Strength of Desire to Smoke (SoD; 24, 25) using a 7 point Likert scale (1-7). SoD and DtS are two frequently used measures of cigarette cravings. DtS is assessed with the following statement: ‘I have a desire for a cigarette right now’ (1 = strongly disagree, 4 = neither agree or disagree, 7 = strongly agree), while SoD was adapted (26) from the Mood and Physical Symptoms Scale (24, 25) and is assessed with the statement ‘How strong is your desire to smoke right now?’ (1 = not at all, 4 = somewhat, 7 = extremely). Studies were eligible if they involved randomised cross-over or parallel arm trials with a minimum abstinence period of two hours prior to baseline measurement, which increases baseline cigarette cravings (27). Acute studies involving participants who were taking part in a cessation programme or were using nicotine replacement therapy (NRT) were excluded since baseline cravings may be low and we sought to determine the effects of PA on strong cravings, as typically experienced during the first hours and days of cessation. To avoid publication bias, we included both published and unpublished studies.

Data extraction and synthesis

Information regarding individual participants’ pre- and post-treatment craving levels (DtS and/or SoD measures) and the conditions they experienced was obtained for all participants in the eligible studies.

To be able to compare PA treatment versus control treatment, all three-arm studies were collapsed into a two-arm design. More specifically, in studies where there were two PA conditions and one

control condition, both PA conditions were pooled into one PA arm. Similarly, if there were two control conditions (and one PA condition) both control conditions were collapsed into one control arm. The majority of studies used a Likert scale of 1-7 to record both SoD and DtS. If a study used a 0-5 Likert scale we adjusted the values (i.e., from 0-5 to 1-7 scale; i.e. 0 = 1, 1 = 2.2, 2 = 3.4 etc up to 5 = 7) and included it in the review (28, 29).

Data analyses

Both fixed effect (FE) meta-analysis methods (which assume that individual studies are estimating the same underlying treatment effect) and random effects (RE) methods (which assume that different studies are estimating different but related effect sizes) were considered. Due to the heterogeneity of studies with regard to types of PA intervention and participant characteristics, the RE methods were applied to the data (30, 31). Although technically ordinal variables rather than continuous, these variables were treated as continuous (as in the primary studies) for the purpose of the analyses, and to facilitate use of linear regression modelling. When using IPD, there are two basic approaches to meta-analyses. The simpler of these is to use a two-stage model, in which an effect size, with related metrics such as the confidence interval or standard error, or aggregate data, can be derived for each primary study and then incorporated using standard meta-analysis methods. Alternatively, a more complex one-stage model can be used in which all data from the primary studies are incorporated into one model, which accounts for the derivation of the data from multiple trials (32). A one-stage model has advantages over a two-stage model when investigating patient-level sources of heterogeneity, as patient-level characteristics can be incorporated into the model (33). For these analyses, both approaches were used; although it was anticipated that results would be similar, the two-stage model allows for the visual presentation of results in the form of forest plots, and for easy quantification of heterogeneity, whilst the use of a one-stage approach facilitates future analyses incorporating patient-level covariates.

Two-stage meta-analyses were performed by initially deriving an effect size (ES) in terms of the mean difference between the PA and control groups for post-intervention SoD/DtS within each trial, using IPD. For parallel arm trials, a linear regression model with SoD/DtS as the outcome variable was used to derive a mean difference between the two treatment arms and its associated standard error (SE) in the first stage. Adjustment was made for baseline SoD/DtS. For cross-over trials, to determine the mean difference and SE, a mixed linear regression model with a random intercept on participant was employed for all trials (to allow adjustment for multiple observations on individual participants; 34) in the first stage. Again, adjustment was made for the baseline value of SoD/DtS. In the second stage, using the derived data from each trial, the results were combined using RE models, to yield a pooled estimate for the average standardised mean difference across the studies. Statistical heterogeneity was also investigated by visual inspection of forest plots and using the Q statistic (with a p-value < 0.1 considered to be significant; 35) and I^2 methods (36).

For the one-stage meta-analyses, studies were combined using a mixed linear regression model (37), with a fixed effect on study and a random intercept on participant (to allow adjustment for multiple observations within participant for the cross-over trials). For a random effect on treatment, a random slope within study was added to the model, allowing the treatment effect to vary across studies. Using a random effects model, an approximate 95% mid-range (assuming a normal distribution of treatment effects across studies) can be derived using the fixed effect (mean difference between groups) for intervention and the standard deviation (SD) for intervention effect within study (38). If the fixed effect is given by a and the SD of the random effect is given by b , then a 95% midrange is given by $a - 1.96b$; $a + 1.96b$. For 95% of studies, the true mean difference between intervention groups lies within this range. All analyses were performed using Stata v. 11.

RESULTS

Literature search

The database searches yielded 544 items. After including studies from other resources, such as a previous review by Taylor et al (11), SRNT meeting abstracts, responses to key list-serves, reference searches, and communication with published authors and excluding duplicates, the first author identified 411 titles. Next, the first author excluded 353 articles (based on the title). Both the first and last author further examined 58 abstracts. Thirty six studies (27-29, 39-71) investigating the effects of various types of PA on cigarette cravings in smokers were identified (Figure 1). However, only 20 studies (27-29, 39, 43, 45, 49, 50, 53-57, 63-65, 67, 68, 70, 71) were found to be eligible and primary authors were contacted to provide raw IPD. We were not able to obtain IPD for one study (71) and thus this study was excluded from the meta-analysis. Tables S1 and S2 summarise the 36 studies investigating acute effects of PA on cigarette cravings (see Supporting Information details given at the end).

Insert Figure 1

Study characteristics and quality assessment

Among the 19 RCTs included in the meta-analysis, seven studies used a parallel arm design (39, 43, 45, 49, 65, 67, 68) and 12 studies used a cross-over design (27-29, 50, 53-57, 63, 64, 70). There were 14 published studies (39, 43, 45, 49, 53-56, 63-65, 67, 68, 70), four PhD projects (27, 29, 50, 57) and one MSc project (28). The duration of the PA/control interventions ranged from 5–40 minutes. The number of participants in each study varied from 10–84. All craving measures were taken immediately before the intervention and immediately after (27-29, 39, 43, 50, 53, 55-57, 63-65, 67, 68, 70) or 5 minutes after the intervention (45, 49, 54). One study (39) delivered two interventions on the same day; the first in a laboratory, which was followed with an ‘outside laboratory’ intervention. To increase homogeneity of the selected studies (all other studies were conducted in a laboratory environment) we included only the laboratory based results.

Studies investigated the effects of moderate-intensity walking (27, 28, 50, 54, 63-65, 70), running (28, 63), moderate-intensity cycling (29, 43, 45, 49, 53, 55-57, 67), vigorous-intensity cycling (29, 49), light cycling (43) and isometric exercise (39, 50, 68). Intensity of PA in studies was described using rating of perceived exertion (RPE; 72), percentage of heart rate (HR) max, HR reserve or a combination of these methods. The study investigating light cycling (43) reported no significant differences in change scores between the light cycling and passive conditions at any point, yet light cycling was coded as PA condition as cycling is a PA by definition. All control conditions were passive. Sixteen studies used sitting passively (27-29, 43, 49, 53-57, 63-65, 67, 68, 70), some control conditions included sitting passively and listening to an audio recording (39, 50), a cognitive task (45), watching a video (67), body scanning techniques (39, 68). Both studies investigating body scanning techniques suggested a positive effect of body scanning on craving reduction (39, 68), yet body scanning was coded as a control condition because it does not involve any bodily movement.

Overall, 13 studies used both DtS and SoD as a measure of cigarette cravings (27-29, 43, 45, 50, 53, 63-65, 67, 68, 70), two studies used only SoD (39, 49) and four studies used only DtS (54-57). Table 1 describes baseline cravings for SoD and DtS for all 19 studies. Three studies reported only one craving measure in their published data (64, 68, 70), while all three studies collected both SoD and DtS measures of cigarette cravings. We were able to obtain IPD for both craving outcomes from the authors (64, 68, 70), and included both SoD and DtS measures in our analyses. In addition, we included craving data from four participants who were excluded from a published dataset as they did not fulfil the requirements for the main outcome of the study (70).

The methodological quality of the studies was also examined. Publication bias was addressed by including both published and unpublished studies. As both SoD and DtS outcomes produced similar results (even if only one of the collected outcomes was published), reporting bias was not considered to be an issue. All studies reported using randomisation in their design; however, one study reported that the randomisation was based on a recruitment order (63).

Insert Table 1 about here

Strength of Desire

SoD was the main outcome in 15 studies providing 797 observations; 440 in PA and 475 in control condition. Seven of these studies were parallel arm studies (39, 43, 45, 49, 65, 67, 68) and eight were cross-over studies (27-29, 50, 53, 63, 64, 70). Five of the parallel arm studies, included three arms in their design (39, 43, 49, 67, 68). Passive and body scanning conditions were both considered to be control arms (39, 68). Similarly, both video watching and the sitting condition were considered to be a control arm in one study (67). We considered both moderate and vigorous cycling to be PA treatment arms (49). Both light and moderate cycling were coded as PA conditions for one study (43). Four of the cross-over design studies (28, 29, 50, 63) included three arms in their design. We combined treadmill running and walking (63), vigorous and moderate cycling (29), treadmill running and walking (28), and treadmill walking and isometric exercise (50), considering all of these conditions as PA.

Desire to smoke

DtS was the main outcome in 17 studies providing 837 observations; 463 in PA and 374 in control condition. Five of these studies were parallel arm studies (43, 45, 65, 67, 68) and 12 were cross-over studies (27-29, 50, 53-57, 63, 64, 70). Three of the parallel arm studies (43, 67, 68) included three arms in their design. Again, we considered passive and body scanning conditions (68), video watching and passive condition (67) to be control conditions and both light cycling and passive condition (43) to be a PA condition. Four of the cross-over design studies (28, 29, 50, 63), included three arms in their design. We combined treadmill running and walking (63), vigorous and moderate cycling (29), treadmill running and walking (28) and treadmill walking and isometric exercise (50).

Individual Participant Data Meta-Analysis

The individual meta-analysis results are summarised in Table 2 and 3 and are appraised in the discussion section.

Insert Table 2 and 3 about here

All eligible studies (both parallel arm and cross-over studies)

Two-stage random effects meta-analysis

A two-stage IPD random effects meta-analysis of 15 studies yielded a summary result (average standardised mean difference across studies) of -1.91 (95% CI:-2.59 to -1.22) for SoD. Similar meta-analysis of 17 studies yielded a summary result of -2.03 (95% CI: -2.60 to -1.46) for DtS. Both analyses showed a high level of between study heterogeneity ($I^2 = 94.2\%$; $Q = 240.35$, $p < 0.001$ and $I^2 = 92.0\%$; $Q = 201.02$, $p < 0.001$, respectively). Figures 2 and 3 show the associated forest plots for SoD and DtS, respectively.

Insert Figure 2 and 3 about here

When analysing published and unpublished studies separately we observed results in the same direction with moderately higher values for DtS than SoD in both published and unpublished studies. A two-stage IPD random effects meta-analysis of 11 published studies with SoD (39, 43, 45, 49, 53, 63-65, 67, 68, 70) yielded a summary result of -1.91 (95% CI:-2.85 to -0.97) and a similar meta-analysis of 12 published studies with DtS (43, 45, 53-56, 63-65, 67, 68, 70) yielded a summary result of -2.13 (95% CI: -2.88 to -1.38). Both analyses showed a high level of between study heterogeneity ($I^2 = 94.9\%$; $Q = 194.28$, $p < 0.001$ and $I^2 = 92.9\%$; $Q = 155.42$, $p < 0.001$, respectively). A two-stage IPD random effects meta-analysis of four unpublished studies with SoD (28, 29, 50, 57) yielded a summary result of -1.90 (95% CI:-2.88 to -0.91) and a similar meta-analysis of five unpublished studies with DtS (27-29, 50, 57) yielded a summary result of -1.81 (95% CI: -2.71 to -0.91). Again,

both analyses showed a high level of between study heterogeneity ($I^2 = 92.9\%$; $Q = 42.22$, $p < 0.001$ and $I^2 = 90.1\%$; $Q = 40.24$, $p < 0.001$, respectively).

One-stage Individual Participant Data Meta-Analysis

A one-stage IPD random effects meta-analysis yielded a fixed effect size (mean difference) of -1.89 (-2.53; -1.26) for SoD (15 studies; 797 observations), with an SD on the associated random effect of 0.850. Hence, the 95% midrange of intervention effects across studies was -3.56; -0.22. For DtS (17 studies; 837 observations), the fixed effect size was -2.03 (95% CI: -2.54 to -1.51), with an SD on the associated random effect of 0.722. This yielded a 95% midrange of intervention effects across studies of -3.45; -0.62.

Parallel arm studies

Two-stage random effects meta-analysis of parallel arm studies

The two-stage IPD random effects meta-analysis of seven parallel arm studies yielded a summary result of -1.78 (95%CI:-3.17 to -0.40) for SoD and the equivalent meta-analysis of five parallel arm studies yielded a summary result of -2.27 (95%CI: -3.82 to -0.72) for DtS. Both analyses showed a high level of between study heterogeneity ($I^2 = 96.5\%$; $Q = 171.32$, $p < 0.001$ and $I^2 = 96.8\%$; $Q = 124.81$, $p < 0.001$, respectively). Figures S1 and S2 show the associated forest plots for SoD and DtS, respectively (see Supporting Information details given at the end).

Studies investigating physical activity of moderate intensity

Because the effect sizes of the individual studies varied, possibly suggesting that the effect of PA may be dependent on the type, intensity or duration of PA used, we decided to analyse only studies comparing moderate intensity PA with a control condition. Altogether 18 studies compared moderate PA (as defined by RPE, HR max or HR reserve in the individual studies) with controls using SoD and/or DtS. These include 16 studies with DtS as the main outcome (27-29, 43, 45, 50, 53-57, 63-65,

67, 70) and 13 studies with SoD as the main outcome (27-29, 43, 45, 49, 50, 53, 63-65, 67, 70). All studies compared either moderate cycling (ten studies) or moderate walking (eight studies) with a control condition.

Two-stage random effects meta-analysis

A two-stage IPD random effects meta-analysis of 13 studies yielded a summary result of -2.20 (95% CI: -2.89 to -1.51) for SoD and an equivalent meta-analysis using DtS including 16 studies yielded a summary result of -2.14 (95% CI: -2.71 to -1.57). Both analyses showed a high level of between study heterogeneity ($I^2 = 92.1\%$; $Q = 152.35$, $p < 0.001$ and $I^2 = 89.7\%$; $Q = 146.05$, $p < 0.001$, respectively). Figures S3 and S4 show the associated forest plots for SoD and DtS, respectively (see Supporting Information details given at the end).

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DISCUSSION

All analyses suggest that short bouts of PA acutely decrease cigarette cravings (Table 2 and 3) and confirm conclusions from previous narrative reviews (10, 11). We were not able to obtain IPD from one study (71); however, as the study included only eight participants, it is unlikely that it would have an effect on the reported results. When the analyses were restricted to parallel arm trials only, we found very similar results compared to analyses including all studies, with cross-over design studies producing effect sizes similar to those of parallel arm design. In addition, there were no substantial differences between the one-stage and two-stage RE meta-analysis results of all studies. Both published and unpublished studies showed similar effects in terms of direction and magnitude. Similar effect sizes for both outcome measures (SoD and DtS) were also found in cases where we were able to obtain IPD for both outcome measures, while only one outcome was reported in the associated publication. When we narrowed the comparison to only moderate-intensity PA versus controls, the effect sizes were somewhat larger. This suggests that the prospective moderating effects of PA

intensity (and possibly type and duration of PA also) on cigarette cravings needs to be further investigated.

Our results were similar to those reported in a recent review (21), despite some differences in methodology. The authors of the review used imputed changes in scores in cravings, did not adjust for baseline values of SoD and DtS, included fewer studies in the meta-analyses (9 and 10 for SoD and DtS respectively) and also included a study with participants using NRT (40). Similarity of the results may suggest that the effects of acute PA on cigarette cravings are robust. The study that produced the largest effect size for both SoD (-4.54; 95% CI:-5.00 to -4.09) and DtS (-4.27; 95% CI:-4.76 to -3.79) reported the highest mean baseline measures (Table 1; 67). This study also used slightly older participants (mean age = 36yrs) than other studies. Two other studies that produced larger effect sizes (effect size > -3; 27, 64), also had high initial cravings (Table 1). However, other studies also had high baseline cravings (i.e., > 5) and did not produce so large effect sizes. In contrast, all studies investigating isometric exercise (39, 50, 68) had the smallest effect sizes, with a 95% CI including 0 in two cases for SoD (39, 68) and in one case for DtS (68). The results from the above mentioned studies further support the idea that mode of PA may influence the effects of short bouts of PA on cravings. In addition, these results may also suggest that age and nicotine dependence (judged by the level of baseline cravings) may moderate the effect of acute PA on cigarette cravings, although further research is warranted to corroborate this suggestion.

In two studies investigating the effect of isometric exercise on cravings we considered both passive and body scanning conditions to be control conditions. However, both studies investigating body scanning suggested a positive effect of body scanning (compared with passive control) on cigarette cravings (39, 68). If the body scanning conditions are removed from the analysis (comparing sitting control condition with PA), the effect sizes of both studies increased (but remained low). When we removed isometric exercise from a study comparing a walking condition and an isometric exercise condition with a control condition (50), the effect size increased. Similarly, when light cycling was

excluded from the analysis (43), the effect size increased. Such results may again suggest that some modes of PA may be less beneficial than others in reducing cigarette cravings, although in some situations (e.g., in a workplace) sitting-based isometric exercise may be more practical than aerobic-type exercise.

Most importantly, all individual studies in all analyses consistently had effect sizes (for both SoD and DtS) in the same direction (varying only in magnitude). All indicated positive effects of PA on cigarette cravings and suggested that it was feasible to quantify the effects of an acute bout of PA on cigarette cravings using meta-analysis. Furthermore, all meta-analyses showed a moderate decrease in cigarette cravings after a short bout of physical activity, which was statistically significant across all meta-analyses. The magnitude of the craving reduction after short bouts of PA is comparable and exceeding the craving reduction associated with NRT and glucose (4, 11), and this may have practical implications for the use of PA as a smoking cessation aid.

CONCLUSIONS

This is the first study to quantify the acute effects of PA on cigarette cravings using IPD meta-analysis. The effects were large, at a time when participants were experiencing moderate to high cravings following a period of abstinence. This review highlights the potential of a single session of PA to reduce cravings, especially when cravings are high. However, further analysis exploring heterogeneity among the studies is needed to improve understanding of the effects of acute PA on cigarette cravings. Investigating the role of patient characteristics, smoking characteristics and aspects of PA such as type, duration and intensity, as potential moderators on the effects is necessary.

Declaration of interest

None.

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References

1. Robinson S., Harris H. *Smoking and drinking among adults, 2009*. A report on the 2009 General Lifestyle Survey. UK: Office for National Statistics; 2011.
2. Hughes J. R., Keely J., Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004; **99**: 29-38.
3. Hughes J. R. How confident should we be that smoking cessation treatments work? *Addiction* 2009; **104**: 1637-40.
4. Cahill K., Stead L. F., Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Syst Rev* 2012; CD006103.
5. Stead L. F., Perera R., Bullen C., Mant D., Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008; CD000146.
6. Hughes J. R., Stead L. F., Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007; CD000031.
7. Farley A. C., Hajek P., Lycett D., Aveyard P. Interventions for preventing weight gain after smoking cessation. *Cochrane Database Syst Rev* 2012; CD006219.
8. Doherty K., Kinnunen T., Militello F.S., Garvey A.J. Urges to smoke during the first month of abstinence: relationship to relapse and predictors. *Psychopharmacology* 1995; **119**: 171-8.
9. Everson, E. S., Taylor, A. H., Ussher, M. Determinants of physical activity promotion by smoking cessation advisors as an aid for quitting: support for the Transtheoretical Model. *Patient Educ Couns* 2010; **78**: 53-6.

10. Ussher M. H., Taylor A. & Faulkner G. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev* 2012; CD002295.
11. Taylor A. H., Ussher M. H., Faulkner G. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect and smoking behaviour: a systematic review. *Addiction* 2007; **102**: 534-43.
12. Chalmers I. The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. *Ann N Y Acad Sci* 1993; **703**: 156-65.
13. Sutton A. J., Higgins J. P. T. Recent developments in meta-analysis. *Stat Med* 2008; **27**: 625-50.
14. Riley R. D., Lambert P. C., Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; **340**: c221.
15. Stewart L. A., Clarke M. J. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. *Stat Med* 1995; **14**: 2057-79.
16. Lyman G. H., Kuderer N. M. The strengths and limitations of meta-analyses based on aggregate data. *BMC Med Res Methodol* 2005; **5**: 14.
17. Higgins J. P. T. & Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester; UK : Wiley-Blackwell; 2008.
18. Stewart L. A., Tierney J. F. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof* 2002; **25**: 76-97.
19. Dwan K., Altman D. G., Arnaiz J. A., Bloom J., Chan A. W., Cronin E. *et al.* Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One* 2008; **3**: e3081.
20. Hopewell S., McDonald S., Clarke M., Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database Syst Rev* 2007; MR000010.
21. Roberts, V., Maddison, R., Simpson, C., Bullen, C., Prapavessis, H. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect, and smoking behaviour: systematic review and meta-analysis. *Psychopharmacology* 2012; **222**: 1-15.

22. Moher D., Liberati A., Tetzlaff J., Altman D. G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.
23. Tiffany S. T., Drobes D. J. The development and initial validation of a questionnaire on smoking urges. *Br J Addict* 1991; **86**: 1467-76.
24. West R., Russell M. Pre-abstinence smoke intake and smoking motivation as predictors of severity of cigarette withdrawal symptoms. *Psychopharmacology* 1985; **87**:334–336.
25. West R., Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology* 2004; **177**:195-9.
26. West R., Courts S., Beharry S., May S., Hajek P. Acute effect of glucose tablets on desire to smoke. *Psychopharmacology* 1999;**147**:319–321.
27. Katomeri M., Taylor A. H. Effects of walking on desire to smoke and withdrawal symptoms during a smoking cue, and ad libitum smoking. Paper presented at ECSS; 2006 Jul; Lausanne, Switzerland.
28. Thompson L. *The effects of an acute bout of moderate and vigorous intensity exercise on smoking cravings, withdrawals, and attentional bias towards smoking-related videos in temporarily abstinent smokers*. MSc dissertation, UK: University of Exeter; 2009.
29. Oh H., Taylor A. H. Exercise reduces desire to smoke and visual attentional bias for cigarettes, but does exercise intensity make a difference. Paper presented at National Smoking Cessation Conference; 2011 Jun; London, UK.
30. Riley R.D., Higgins J.P., Deeks J.J. Interpretation of random effects meta-analyses. *BMJ* 2011; **342**: d549.
31. Borenstein M., Hedges L. V., Higgins J. P. T., Rothstein H. R. *Introduction to Meta-Analysis*. UK: Wiley & Sons Ltd; 2009.
32. Simmonds M.C., Higgins J.P.T., Stewart L.A., Tierney J.F., Clarke M.J., Thompson S.G. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clinical Trials* 2005; **2**:209–217.

33. Lambert P.C., Sutton A.J., Abrams K.R., Jones D.R. A comparison of summary patient level covariates in metaregression with individual patient data meta-analysis. *Journal of Clinical Epidemiology* 2002; **55**: 86–94.
34. Brown H., Prescott R. *Applied Mixed Models in Medicine*. Chichester, UK: John Wiley & Sons Ltd; 1999.
35. Sutton A. J., Abrams K. R., Jones, D. R., Sheldon, T. A., Song F. Systematic reviews of trials and other studies. *Health technol Assess* 1998; **2**.
36. Higgins J. P., Thompson S. G. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-58.
37. Higgins J. P., Whitehead A., Turner R. M., Omar R. Z., Thompson S.G. Meta-analysis of continuous outcome data from individual patients. *Stat Med* 2001; **20**: 2219-41.
38. Lyratzopoulos G., Elliott M., Barbiere J. M., Henderson A., Staetsky L., Paddison C. *et al*. Understanding ethnic and other socio-demographic differences in patient experience of primary care: evidence from the English General Practice Patient Survey. *BMJ Qual Saf* 2012; **21**: 21-9.
39. Ussher M., Cropley M., Playle S., Mohidin R., West R. Effect of isometric exercise and body scanning on cigarette cravings and withdrawal symptoms. *Addiction* 2009; **104**: 1251-7.
40. Arbour-Nicitopoulos K. P., Faulkner G. E., Hsin A. Acute exercise, craving reduction and affect among individuals with serious mental illness. Paper presented at SRNT; 2011 Feb; Toronto, Canada.
41. Bock B. C., Marcus B. H., King T. K., Borrelli B., Roberts M.R. Exercise effects on withdrawal and mood among women attempting smoking cessation. *Addict Behav* 1999; **24**: 399-410.
42. Daley A. J., Oldham A. R. H., Townsom, M. The effect of acute exercise on affective responses and desire to smoke in sedentary temporarily abstaining smokers: a preliminary study. *J Sport Sci* 2004; **22**: 303-4.
43. Daniel J., Cropley M., Ussher M., West R. Acute effects of a short bout of moderate versus light intensity exercise versus inactivity on tobacco withdrawal symptoms in sedentary smokers. *Psychopharmacology* 2004; **174**: 320-6.

44. Daniel J. *The effects of acute exercise on short term smoking withdrawal symptoms and desire to smoke*. PhD thesis, Study 3b, UK: University of Surrey; 2005.
45. Daniel J. Z., Cropley M., Fife-Schaw C. The effect of exercise in reducing desire to smoke and cigarette withdrawal symptoms is not caused by distraction. *Addiction* 2006; **101**: 1187-92.
46. Daniel J. Z., Cropley M., Fife-Schaw C. Acute exercise effects on smoking withdrawal symptoms and desire to smoke are not related to expectation. *Psychopharmacology* 2007; **195**: 125-9.
47. Elibero A., Janse Van Rensburg K., Drobos D. J. Acute effects of aerobic exercise and hatha yoga on craving to smoke. *Nicotine Tob Res* 2011; **13**: 1140-8.
48. Everson E. S., Daley A. J., Ussher M. Does exercise have an acute effect on desire to smoke, mood and withdrawal symptoms in abstaining adolescent smokers? *Addict Behav* 2006; **31**: 1547-58.
49. Everson E. S., Daley A. J., Ussher M. The effects of moderate and vigorous exercise on desire to smoke, withdrawal symptoms and mood in abstaining young adult smokers. *Ment Health Physl Act* 2008; **1**: 26-31.
50. Haasova M., Oh H., Taylor A. T. The acute effects of brisk walking and isometric exercise versus rest on cigarette cravings and attentional bias. Paper presented at ASH Wales; 2011 Oct; Cardiff, UK.
51. Harper T. *Mechanisms behind the success of exercise as an adjunct quit smoking aid*. PhD thesis, Study 1, Canada: The University of Western Ontario; 2011a.
52. Harper T. *Mechanisms behind the success of exercise as an adjunct quit smoking aid*. PhD thesis, Study 2, Canada: The University of Western Ontario; 2011b.
53. Janse Van Rensburg K., Taylor A. H., Hodgson T., Benattayallah A. The effects of exercise on cigarette cravings and brain activation in response to smoking-related images. *Psychopharmacology* 2012;**221**:659-66.
54. Janse Van Rensburg K., Taylor A.H. The effects of acute exercise on cognitive functioning and cigarette cravings during temporary abstinence from smoking. *Hum Psychopharmacol* 2008; **23**: 193-9.

55. Janse Van Rensburg K., Taylor A., Hodgson T. The effects of acute exercise on attentional bias towards smoking-related stimuli during temporary abstinence from smoking. *Addiction* 2009; **104**: 1910-7.
56. Janse Van Rensburg K., Taylor A., Hodgson T., Benattayallah A. Acute exercise modulates cigarette cravings and brain activation in response to smoking-related images: an fMRI study. *Psychopharmacology* 2009; **203**: 589-98.
57. Janse Van Rensburg K., Taylor A. H., Lavric A., Elchlepp H. The acute effects of exercise on event-related potential in response to smoking images; in preparation.
58. Janse Van Rensburg K., Taylor A. H., Hodgson T., Drobles D., Benattayallah A. Can exercise attenuate cue-creativity to smoking images: an fMRI study. *SRNT*; 2011 February; Toronto, Canada.
59. Katomeri M. *Acute effects of self-paced walking on smoking withdrawal and cravings*. PhD thesis, Study 4, UK: University of Plymouth; 2009.
60. Mikhail C. *The acute effects of aerobic exercise on cigarette smoking behaviour*. MSc thesis, Canada: University of Lethbridge; 1983.
61. Pomerleau O. F., Scherzer H. H., Grunberg N.E. The effects of acute exercise on subsequent cigarette smoking. *J Behav Med* 1987; **10**: 117-28.
62. Reeser K. A. *The effects of repeated aerobic and non-aerobic exercise on cigarette smoking*. MSc thesis, Canada: University of Alberta; 1983.
63. Scerbo F., Faulkner G., Taylor A. & Thomas S. Effects of exercise on cravings to smoke: The role of exercise intensity and cortisol. *J Sports Scie* 2010; **28**: 11-9.
64. Taylor A.H., Katomeri M., Ussher M. Acute effects of self-paced walking on urges to smoke during temporary smoking abstinence. *Psychopharmacology* 2005; **181**: 1-7.
65. Taylor A., Katomeri M. Walking reduces cue-elicited cigarette cravings and withdrawal symptoms, and delays ad libitum smoking. *Nicotine Tob Res* 2007; **9**: 1183-90.
66. Thayer R. E., Peters D. P., Takahashi P. J., Birkhead-Flight A. M. Mood and behaviour (smoking and sugar snacking) following moderate exercise: A partial test of self-regulation theory. *Pers and Individ Dif* 1993; **14**: 97-104.

67. Ussher M., Nunziata P., Copley M., West R. Effect of a short bout of exercise on tobacco withdrawal symptoms and desire to smoke. *Psychopharmacology* 2001; **158**: 66-72.
68. Ussher M., West R., Doshi R., Sampuran A.K. Acute effect of isometric exercise on desire to smoke and tobacco withdrawal symptoms. *Hum Psychopharmacol* 2006; **21**: 39-46.
69. Williams D. M., Whiteley J. A., Dunsiger S., Jennings E.G., Albrecht A.E., Ussher M.H. *et al.* Moderate intensity exercise as an adjunct to standard smoking cessation treatment for women: a pilot study. *Psychol Addict Behav* 2010; **24**: 349-54.
70. Faulkner G. E., Arbour-Nicitopoulos K. P., Hsin A. Cutting down one puff at a time: The acute effects of exercise on smoking behaviour. *J Smok Cessat* 2010; **5**: 130-5.
71. Ho, J. *Effect of resistance exercise on the HPA axis and cardiovascular responses to psychological stress during short-term smoking abstinence in men.* PhD thesis, USA: University of Connecticut; 2009.
72. Borg G. A. V. *Borg's Perceived Exertion and Pain Scales.* Champaign, IL: Human Kinetics; 1998.
73. Hughes, J. R., Hatsukami, D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986; **60**: 289-294.
74. Fagerström, K. O. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict Behav* 1978; **3**: 235-41.
75. Cox, L. S., Tiffany, S. T., Christensen, A. G. Evaluation of the brief questionnaire of Smoking Urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 2001; **3**: 7-16.
76. Shiffman, S. M., Jarvik, M. E. Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology* 1976; **5**: 35-9.
77. Shiffman, S. M., Shadel, W. G., Niaura, R., Khayrallah, M. A., Jorenby, D. E., Rayn C. F. *et al.* Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. *Psychopharmacology* 2003; **166**: 343-50.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Strength of Desire to smoke (SoD); Individual Participant Data Meta-analysis of only parallel arm design studies using 2- stage random effects regression of post SoD with study and baseline adjustment.

Figure S2 Desire to Smoke (DtS); Individual Participant Data Meta-analysis of only parallel arm design studies using 2- stage random effects regression of post DtS with study and baseline adjustment.

Figure S3 Strength of Desire to smoke (SoD); Individual Participant Data Meta-analysis comparing control condition with moderate physical activity, using 2-stage random effects regression of post SoD with study and baseline adjustment.

Figure S4 Desire to Smoke (DtS); Individual Participant Data Meta-analysis comparing control condition with moderate physical activity, using 2-stage random effects regression of post DtS with study and baseline adjustment.

Table S1 Summary of studies included in quantitative synthesis.

Table S2 Summary of studies excluded from quantitative synthesis.

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Figure 1: Flow diagram of study retrieval process

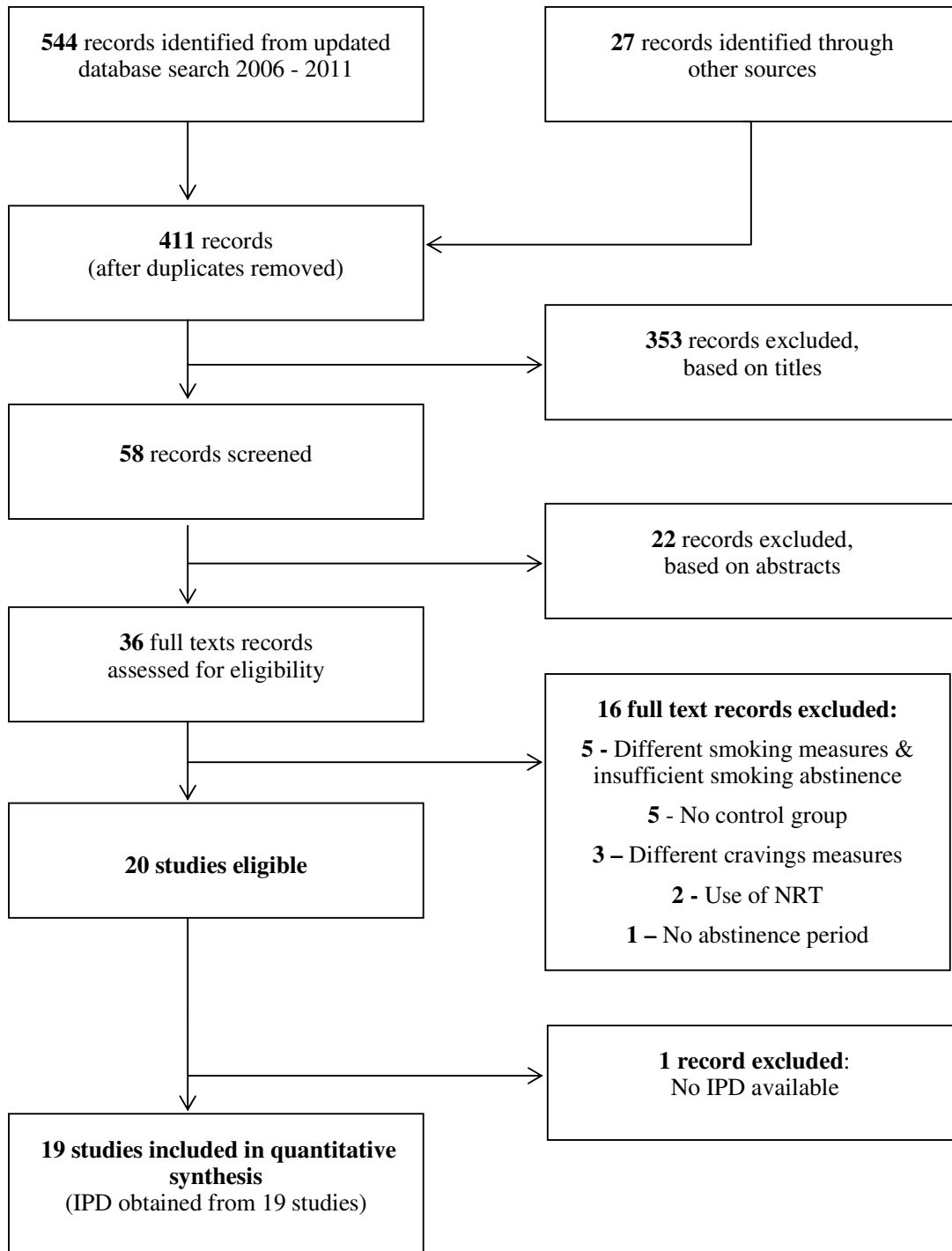
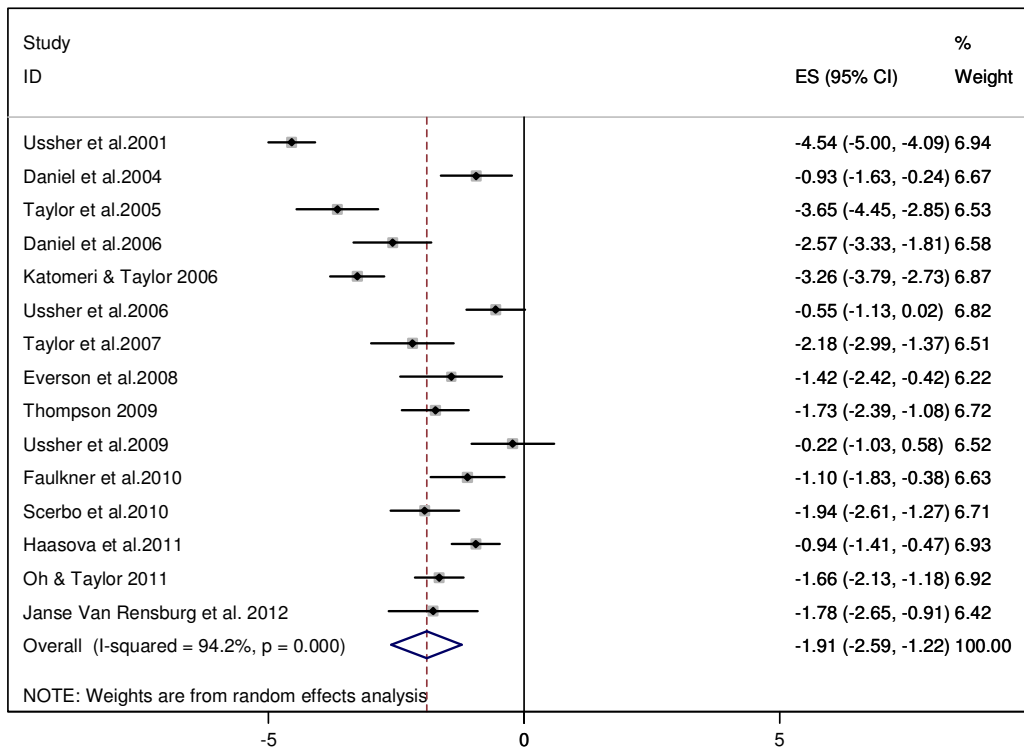
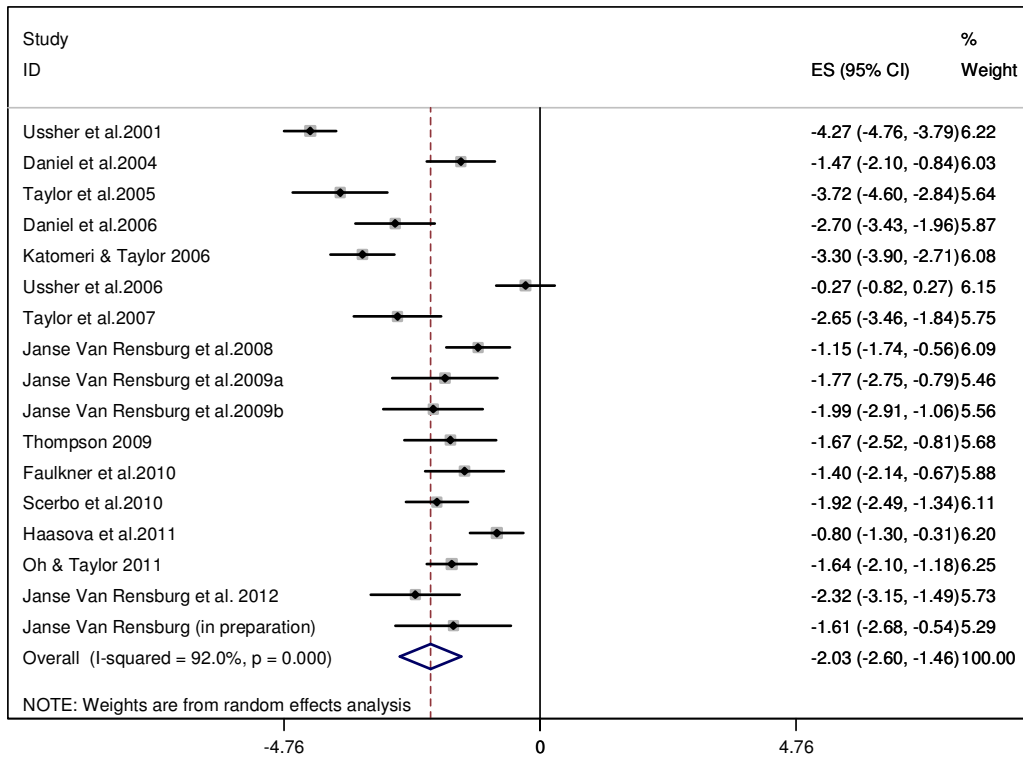


Figure 2: Strength of Desire to smoke (SoD); Individual Participant Data Meta-analysis of all studies using 2- stage random effects regression of post SoD with baseline adjustment.



Notes: Negative ES favours intervention and positive ES favours control condition.

Figure 3: Desire to Smoke (DtS); Individual Participant Data Meta-analysis of all studies using 2-stage random effects regression of post DtS with study and baseline adjustment.



Notes: Negative ES favours intervention and positive ES favours control condition.

Table 1: Mean and SD for baseline and post exercise measures of Strength of Desire and Desire to Smoke.

Study	Strength of desire to smoke				Desire to smoke			
	PA condition Mean (SD)		Controls Mean (SD)		PA condition Mean (SD)		Controls Mean (SD)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Ussher <i>et al.</i> 2001	6.62 (1.01)	2.10 (1.19)	6.22 (1.10)	6.58 (0.77)	6.64 (0.58)	2.31 (1.33)	6.25 (0.77)	6.36 (0.76)
Daniel <i>et al.</i> 2004	3.77 (1.68)	2.68 (1.69)	3.82 (2.02)	3.64 (2.18)	3.70 (1.73)	2.16 (1.26)	4.11 (1.87)	3.82 (2.13)
Taylor <i>et al.</i> 2005	5.87 (1.41)	2.13 (1.06)	5.67 (1.29)	5.73 (1.22)	6.07 (1.62)	1.80 (0.86)	6.20 (1.01)	5.53 (1.55)
Daniel <i>et al.</i> 2006	4.10 (1.71)	2.35 (1.50)	4.35 (1.46)	5.05 (1.43)	4.35 (1.66)	2.35 (1.35)	4.60 (1.31)	5.15 (1.31)
Katomeri & Taylor 2006	5.40 (1.57)	2.33 (0.96)	5.00 (1.23)	5.53 (1.14)	5.40 (1.45)	2.47 (1.20)	4.90 (1.49)	5.77 (1.10)
Ussher <i>et al.</i> 2006	5.15 (1.81)	4.20 (1.99)	4.45 (1.85)	4.18 (1.77)	5.40 (1.88)	4.60 (1.82)	4.70 (2.00)	4.30 (1.91)
Taylor <i>et al.</i> 2007	4.06 (1.26)	2.87 (1.77)	4.66 (1.40)	5.24 (1.41)	5.00 (1.46)	2.81 (1.96)	5.10 (1.37)	5.48 (1.18)
Everson <i>et al.</i> 2008	4.97 (1.67)	3.23 (1.85)	4.27 (1.44)	4.27 (1.67)	NA	NA	NA	NA
Janse Van Rensburg <i>et al.</i> 2008	NA	NA	NA	NA	4.87 (1.18)	4.09 (1.44)	5.00 (1.17)	5.30 (0.97)
Janse Van Rensburg <i>et al.</i> 2009a	NA	NA	NA	NA	5.15 (1.76)	3.15 (2.21)	5.40 (1.35)	5.05 (1.50)
Janse Van Rensburg <i>et al.</i> 2009b	NA	NA	NA	NA	4.80 (1.48)	3.10 (1.45)	4.40 (1.84)	4.80 (1.69)
Thompson & Taylor 2009	3.82 (1.19)	2.57 (1.31)	3.64 (1.10)	4.24 (0.99)	3.76 (1.79)	2.50 (1.86)	4.00 (1.41)	4.24 (1.70)
Ussher <i>et al.</i> 2009	5.50 (1.45)	3.71 (1.33)	5.18 (1.59)	3.82 (1.40)	NA	NA	NA	NA
Faulkner <i>et al.</i> 2010	4.52 (2.06)	3.43 (1.83)	4.70 (2.01)	4.65 (2.17)	4.78 (1.95)	3.43 (1.70)	4.83 (1.92)	4.87 (1.98)
Scerbo <i>et al.</i> 2010	5.28 (1.45)	3.14 (1.71)	5.78 (1.17)	5.22 (1.31)	5.39 (1.38)	3.25 (1.65)	5.39 (1.58)	5.17 (1.29)
Oh & Taylor 2011	4.08 (1.23)	2.54 (0.82)	4.03 (1.44)	4.18 (1.47)	4.05 (1.21)	2.57 (0.87)	3.97 (1.34)	4.18 (1.38)
Haasova <i>et al.</i> 2011	4.58 (1.75)	3.85 (1.67)	4.45 (1.73)	4.70 (1.72)	4.68 (1.94)	3.85 (1.79)	4.55 (1.88)	4.55 (1.93)
Janse Van Rensburg <i>et al.</i> 2012	5.00 (1.32)	3.67 (1.64)	5.12 (1.41)	5.38 (1.02)	5.28 (1.23)	3.39 (1.54)	5.28 (1.23)	5.71 (0.77)
Janse Van rensburg (in preparation)	NA	NA	NA	NA	4.62 (1.61)	3.69 (2.18)	5.00 (1.21)	5.58 (0.90)

IPD META-ANALYSIS: PA AND CIGARETTE CRAVINGS

Notes: values may differ from the values reported in original articles as we collapsed three-arm designs into two-arm designs, obtained some unpublished IPD and adjusted the outcome measurement scale from two studies (details in the methods section).

Table 2: Meta- analyses of Strength of Desire to smoke.

MA	Designs	Comparison	N	ES (95% CI)	p values	I ² (%)
Two-stage	Parallel & Cross-over	Control v. All PA N = 16	797	-1.91 (-2.59,-1.22)	<0.001	94.2
	Parallel	Control v. All PA N = 8	415	-1.78 (-3.17,-0.40)	<0.001	96.5
	Parallel & Cross-over	Control v. Moderate PA N = 14	603	-2.20 (-2.89,-1.51)	<0.001	92.1
One-stage	Parallel & Cross-over	Control v. All PA N = 16	797	-1.89 (-2.52, -1.26)	<0.001	NA

Notes: CI = Confidence Interval, ES = Effect Size, MA = meta-analysis, N = number of observations, I² = heterogeneity measure, p values from Q-statistic. Negative ES favours intervention and positive ES favours control condition.

Table 3: Meta- analyses of Desire to Smoke.

MA	Designs	Comparison	N	ES (95% CI)	p values	I ² (%)
Two-stage	Parallel & Cross-over	Control v. All PA N = 17	837	-2.03 (-2.60,-1.46)	<0.001	92.0
	Parallel	Control v. All PA N = 5	322	-2.27 (-3.82,-0.72)	<0.001	96.8
	Parallel & Cross-over	Control v. Moderate PA N = 16	706	-2.14 (-2.71,-1.57)	<0.001	89.7
One-stage	Parallel & Cross-over	Control v. All PA N = 17	837	-2.03 (-2.54,-1.51)	<0.001	NA

Notes: CI = Confidence Interval, ES = Effect Size, MA = meta-analysis, N = number of observations, I² = heterogeneity measure, p values from Q-statistic. Negative ES favours intervention and positive ES favours control condition.