The effects of physical activity on cigarette cravings

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: ……..

Abstract

Rationale: Cigarette cravings are one of the most important clinical phenomena in tobacco addiction. A wide range of studies and research designs may help to increase understanding of the relationship between physical activity (PA) and cigarette cravings. **Aims:** (i) To investigate the acute effects of walking and isometric exercise on cigarette cravings, withdrawal, and attentional bias among temporarily abstaining smokers. (ii) To quantify the effects of short bouts of PA on cigarette cravings among temporarily abstaining smokers. (iii) To examine who most benefits from PA, whether changes in affect mediate these effects, and whether a specific attribute of PA is associated with cravings. (iv) To investigate whether any association between habitual PA and cravings in smokers could be found. **Methods:** A randomised controlled crossover trial with three arms addressed aim (i). A systematic review of literature and individual participant data meta-analysis using hierarchical modelling addressed aims (ii) and (iii). Aim (iv) was achieved by using linear regression modelling of cross-sectional data from a smoking cessation study. **Results:** No difference in cravings, withdrawal, and attentional bias between walking and isometric exercise versus control was found. Bouts of PA decreased cigarette cravings by approximately 30%. Moderate intensity PA provided increased benefit when compared with light intensity, whereas vigorous intensity did not confer additional benefits compared with moderate intensity PA. Also bouts of medium (10 minutes) and longer duration (≥15minutes) appeared to be more effective than short duration (≤ 5 min). No moderators and mediators of this association were identified. Habitual moderate intensity PA was the strongest predictor of cigarette cravings in smokers, MPSS was an additional predictor and alcohol consumption moderated the effects of habitual PA on cravings. **Conclusion**: Moderate intensity PA could be recommended to smokers to help decrease cigarette cravings.

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Thank You,

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List of Abbreviations

CI = Confidence Intervals

CO = Carbon Monoxide

CONSORT = CONsolidated Standards of Reporting Trials

CWS = Cigarette Withdrawal Scale

DSM-III = Diagnostic and Statistical Manual of Mental Disorders 3rd edition

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition

DSM-V = Diagnostic and Statistical Manual of Mental Disorders 5th edition

DtS = Desire to Smoke

FTCD = Fagerström Test of Cigarette Dependence

ICD-10 = International Classification of Diseases and related health problems 10th revision

IQR = Inter Quartile Range

MOOSE = The Meta-analyses of Observational Studies in Epidemiology

MPSS = Mood And Physical Symptoms Scale

MWS = Minnesota Withdrawal Scale

NICE = National Institute for Health and Clinical Excellence

NIHR = The National Institute for Health Research

NRT = Nicotine Replacement Therapy

PA = Physical Activity

POMS = Profile of Mood State

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSS = Perceived Stress Scale

QUOROM = The Quality of Reporting of Meta-analyses

QSU = Questionnaire on Smoking Urges

QSU-brief = Brief Questionnaire on Smoking Urges

RR= Risk Ratio

SD = standard deviation

SJWS = Shiffman-Jarvik Withdrawal Scale

SoD = Strength of Desire to smoke

SoU = Strength of Urge to smoke

TCQ = Tobacco Craving Questionnaire

WHO = World Health Organisation

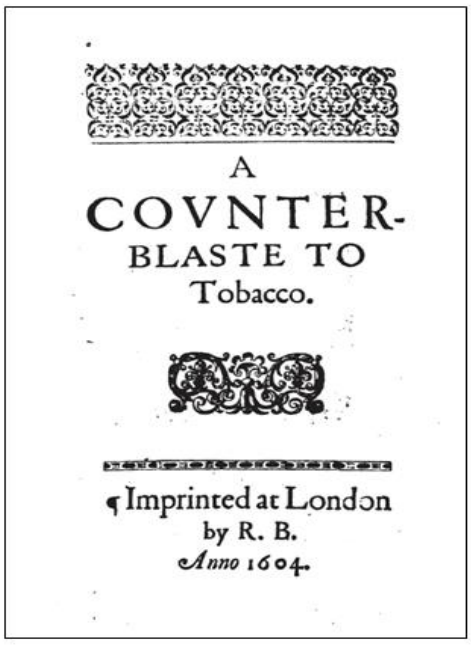
WSWS = Wisconsin Smoking Withdrawal Scale

Chapter 1: Introduction

The first section of this chapter outlines the background and current issues, while the second section lists the aims and objectives of this research. Finally, the last section includes an outline of the remaining chapters of the thesis.

1.1. Background

... A custome lothsome to the eye, hatefull to the Nose, harmefull to the braine, dangerous to the Lungs, and in the blacke stinking fume thereof, neerest resembling the horrible Stigian smoke of the pit that is bottomlesse.


A
COVNTER-
BLASTE TO
Tobacco.

¶ Imprinted at London
by R. B.
Anno 1604.

Figure 1 A cover page and a quote (page D2) from "A Counterblast to Tobacco" by King James I, 1604

Cigarette smoking is the single largest cause of disability and premature death in Britain (Royal College of Physicians 2000). In the past, people's beliefs

about the effects of smoking varied dramatically. Smoking was praised as a cure for headaches and recommended in pregnancy to reduce pain; however, it was punishable by death in some countries in the 16th and 17th century (Orford 1986). The above quote (**Figure 1**) represents the final lines of King James' anti-smoking appeal "A Counterblast to Tobacco" from 1604 (King James I. 1604). Today, there is no doubt about the devastating impact of smoking on health and psychological wellbeing and about the benefits of quitting smoking. Smoking is the most important lifestyle behaviour that contributes to poor health and premature mortality. Almost one fifth of all deaths in England were estimated to be caused by smoking (Eastwood 2012).

To illustrate the effects of smoking, on average a 35-year-old male smoker can expect to die more than 7 years earlier than a man who has never smoked. Similarly, a 35-year-old female smoker will be expected to die 6 years earlier than a woman who has never smoked. Encouragingly, the figures for ex-smokers lie between the two, closer to never smokers than to current smokers (Royal College of Physicians 2000). Quitting smoking is challenging. Unaided attempts to quit have only a 3–5% success rate of 6–12 months' abstinence (Hughes et al. 2004). It has been well established that standard smoking cessation treatments, combining pharmacological and behavioural support, work well (Hughes 2009). Nonetheless, the success rates remain low, with fewer than a third of people quitting successfully even with the best available support (Cahill et al. 2012; Fiore et al. 2008; Hughes et al. 2007; Stead et al. 2008); see **Table 1** for more details.

Table 1 Risk ratios for treatment in meta-analyses of smoking cessation strategies and naively calculated abstinence rates of cessation strategies (%)

Cessation strategy	Maintained abstinence at least 6 months		
	RR (95% CI)	% [c]	% [h]
Unassisted [a]	**1**	**NA**	**3–5**
Placebo [b]	**1**	**13.8**	**NA**
Any NRT	1.58 (1.50 to 1.66)[d]	21.8	7.9
Nicotine gum	1.43 (1.33 to 1.53)[d]	19.7	7.2
Nicotine patch	1.66 (1.53 to 1.81)[d]	22.9	8.3
Nicotine inhaler	1.90 (1.36 to 2.67)[d]	26.2	9.5
Oral NRT	2.00 (1.63 to 2.45)[d]	27.4	10.0
Nicotine nasal spray	2.02 (1.49 to 3.73)[d]	27.9	10.1
Bupropion	1.69 (1.53 to 1.85)[f]	23.3	8.5
Varenicline	2.27 (2.02 to 2.55)[g]	31.3	11.4
Physician advice to quit	Compared with no advice group of 7.9% abstinence rate: OR 1.30 (1.10 to 1.60) [e]		10.2 [e] (8.5–12.0)
Medication and counselling	Compared with medication alone of 21.7% abstinence rate: OR 1.4 (1.20 to 1.60) [e]		27.6 [e] (25.0–30.3)

Notes: a = unassisted absolute values of 3-5 % as reported in Hughes and colleagues, (Hughes et al. 2004); b = placebo value of 13.8% as reported in Fiore and colleagues (Fiore et al. 2008); c = absolute values (%) for cessation strategies were naively calculated using a specific cessation strategy RR (Cahill et al. 2012; Hughes et al. 2007; Stead et al. 2008), and compared with the placebo value of 13.8% (Fiore et al. 2008); d = reported in Stead and colleagues (Stead et al. 2008); e = reported (not calculated) in Fiore and colleagues (Fiore et al. 2008); f = reported in Hughes and colleagues (Hughes et al. 2007); g = reported in Cahill and colleague, 2012 (Cahill et al. 2012); h = absolute values (%) for cessation strategies were naively calculated using a specific cessation strategy RR (Cahill et al. 2012; Fiore et al. 2008; Hughes et al. 2007; Stead et al. 2008), and compared with the unassisted absolute values of 5% (Hughes et al. 2004); NA = not applicable; NRT = nicotine replacement therapy; RR = risk ratio; OR = odds ratio.

While most current smokers want to give up smoking (Eastwood 2012), they find it difficult to curb their cravings in a smoking cessation attempt. These symptoms directly cause distress and can deter quit attempts. Relief of cravings and withdrawal is beneficial to smokers attempting to quit or self-regulate smoking (Shiffman et al. 2004). Data from a large cessation trial showed that, at 6 months after a quit date, a small proportion of ex-smokers still reported strong urges to smoke, while a third of ex-smokers experienced some urges even at

12 months after a quit date (Ussher et al. 2013). In addition, ex-smokers also report cue induced cravings (Carter and Tiffany 1999), with attentional bias measures being an indication of cigarette wanting behaviour in response to salient stimuli (e.g. cigarettes displayed in a shop; Field et al. 2009a).

Apart from traditional cessation strategies (**Table 1**), alternative approaches such as hypnotherapy, acupuncture, acupressure, laser therapy and electro-stimulation are used as aids in smoking cessation. Recent reviews concluded that there is not enough good quality evidence to draw conclusions about the use of these strategies in smoking cessation, although it appears that even if such effects exists they are less effective compared with nicotine replacement therapy (Barnes et al. 2010; White et al. 2011).

Finally, physical activity (PA) has been used as an aid in smoking cessation. PA is currently accepted as a cessation aid by some smokers (Everson-Hock et al. 2010) and is used in some stop-smoking clinics (Everson et al. 2010). However, the role of PA in smoking cessation is not clear (Ussher et al. 2012). There is some evidence that PA can acutely decrease cigarette cravings; short bouts of PA ranging from 5-30 minutes acutely decreased self-reported measures of cigarette cravings and withdrawal (Taylor et al. 2007; Ussher et al. 2012). Yet the size of the effects has not been systematically quantified, and the mechanisms underlying the effects of acute PA on cigarette cravings have not been identified. In addition, the effects of habitual PA on general cigarette cravings have not been investigated.

1.2. Aims

A good understanding of the relationship between PA and cigarette cravings is needed to better understand how best to promote PA to smokers attempting to quit. This thesis examines the relationship between PA and cigarette cravings using a range of methods including an original acute study, meta-analysis, multilevel-modelling, and linear regression analysis of cross-sectional data. The effects of acute PA on cigarette cravings are quantified and the effects of potential moderators and mediators on the relationship between PA and cigarette cravings are investigated. Characteristics of smokers who may benefit to a greater or lesser extent (with regard to cigarette cravings) from acute PA are identified. In addition, to extend the understanding from acute studies, the relationship between cigarette cravings and habitual PA levels in a sample of smokers is investigated. In summary, this thesis focuses on the following four aims:

I. To determine whether PA is more effective (compared with a passive condition) in reducing cigarette cravings among temporarily abstaining smokers, and whether there are any differences between the effects of walking and isometric (ISO) exercise.

II. To determine the effects of a short bout of PA on cigarette cravings among temporarily abstaining smokers using individual participant data (IPD) meta-analysis.

III. To determine who most benefits from PA and whether changes in affect mediate these effects, and whether any attributes of PA are

associated with cigarette cravings among temporarily abstaining smokers.

IV. To determine the effects of habitual PA on cigarette cravings in smokers.

1.3. Thesis Outline

Study 1: The effects of brisk walking and seated isometric exercise on cigarette cravings and attentional bias to smoking cues.

Chapter 4 investigates the effects of brisk walking and seated ISO exercise on cigarette cravings, withdrawal and attentional bias to smoking cues compared with a rest condition among temporarily abstaining smokers using a cross-over randomised controlled trial. The results have been presented in Cardiff in 2011 at the Action on Smoking and Health (ASH) Wales conference; Appendix A **Figure 23** (Haasova et al. unpublished).

Study 2: The acute effects of physical activity on cigarette cravings: Systematic review and individual participant data meta-analysis.

Chapter 5 investigates the effects of short bouts of PA on cigarette cravings in temporarily abstaining smokers. A systematic review of the literature identified acute randomised controlled trials examining the effects of acute PA on cigarette cravings among temporarily abstaining smokers. Cigarette cravings, demographic, and PA IPD from eligible studies were extracted. The effects of PA on cravings were quantified using IPD meta-analyses. The results of this chapter were presented at The European College of Sport Science (ECSS) conference in Liverpool, UK in 2012 (Appendix A **Figure 24**) and published (Haasova et al. 2013; Appendix A page 200).

Study 3: The acute effects of physical activity on cigarette cravings: Exploration of potential moderators, mediators and physical activity attributes using systematic review and individual participant data meta-analyses.

Chapter 6 investigates potential moderators and mediators of the effects of PA on cigarette cravings among temporarily abstaining smokers. It examines the demographic and smoking characteristics that may be associated with greater or lesser benefits from PA, whether changes in affect mediate these effects, and whether specific attributes of PA are associated with cigarette cravings. The IPD from randomised controlled trials collated in Study 2 are utilised. The results of this chapter were published (Haasova et al. 2014; Appendix A page 201) and presented at The Society for Research on Nicotine and Tobacco (SRNT) conference in Boston, USA in 2013 (Appendix A **Figure 25**).

Study 4: How habitual physical activity and other individual characteristics are associated with cigarette cravings: An exploration of baseline measures from the Exercise Assisted Reduction then Stop smoking study.

Chapter 7 investigates the relationship between habitual PA and general cigarette cravings in smokers who are not temporarily abstaining from cigarettes. In addition, the effects of demographic variables and background variables were also considered. Baseline cross-sectional data collected in the Exercise Assisted Reduction then Stop smoking study (EARS) are analysed using linear regression models (manuscript in preparation).

Chapter 2: Literature Review

The first section of this chapter discusses the nature of tobacco addiction, the second section examines the role of cigarette cravings in tobacco addiction and reviews how cigarette cravings are measured. Finally, the last section summarises the implications of the literature for the four aims stated in Chapter 1.

2.1 Tobacco addiction

It is believed that nicotine is the main cause of smoking addiction (Royal College of Physicians 2000). However, it is well acknowledged that it is not nicotine alone that is to blame for tobacco addiction (Gifford and Humphreys 2007; West 2006). There are many addiction theories, but in this thesis, tobacco addiction in relation to the two most common sets of criteria in substance addiction, the Diagnostic and Statistical Manual of Mental Disorders-5th edition (American Psychiatric Association 2000) and the International Classification of Diseases and related health problems-10th revision (ICD-10; World Health Organisation 1990), will be considered.

Despite “addiction” being one of the most important concepts in behavioural and clinical science, there are many different definitions. In addition, two terms, “addiction” and “dependence”, are often used interchangeably. O’Brien and colleagues (2006) suggested that the term

dependence was traditionally used to describe physical dependence (i.e. the physiological adaptation to repeated dosing of medication), which may occur also in the absence of addiction (O'Brien et al. 2006). Similarly, West describes addiction as impaired control, and physical dependence as a state of physiological adaptation to a drug which then needs to be taken to prevent withdrawal symptoms (West 2006).

Tobacco addiction is defined as tobacco use disorder in DSM-V. Tobacco use disorder replaced the DSM-IV two separate categories, nicotine abuse and nicotine dependence. Tobacco use disorder is manifested by at least two of the following (occurring within a 12-month period); two to three criteria indicate a mild disorder, four to five criteria indicate a moderate disorder, and six and more criteria indicate a severe disorder:

1. recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home;
2. recurrent substance use in situations in which it is physically hazardous;
3. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance;
4. tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect or (b) a markedly diminished

effect with continued use of the same amount of the substance;

5. withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance; or (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms;

6. the substance is often taken in larger amounts or over a longer period than was intended;

7. there is a persistent desire or unsuccessful efforts to cut down or control substance use;

8. a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;

9. important social, occupational, or recreational activities are given up or reduced because of substance use;

10. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance; and

11. craving or a strong desire or urge to use a specific substance.

Similarly, tobacco addiction is defined as tobacco dependence syndrome in ICD-10 (this version is being currently revised). Tobacco dependence

syndrome is manifested by at least three of the following (occurring together at some point during the previous year):

1. a strong desire or sense of compulsion to take the substance;
2. difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3. a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses;
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects; and
6. persisting with substance use despite clear evidence of overtly harmful consequences.

Both diagnostic criteria, DSM-V and ICD-10, combine indications of harmful substance use and, physiological and psychological dependence in

their definitions. However, the presence of physiological dependence is not required for a diagnosis of tobacco addiction.

2.2 The role of cigarette cravings in tobacco addiction

Cigarette cravings are believed to have a key role in tobacco addiction (Robinson and Berridge 1993). Psychological disturbances in smokers attempting to quit, such as cravings and withdrawal symptoms can negatively influence the success of such attempts (Shiffman et al. 2004). A relief of these disturbances is beneficial, this is specifically advantageous in the first week of abstinence as adverse symptoms are the most severe (Hughes et al. 2004). In fact, all major theories of drug dependence propose that cravings are important for understanding drug use motivation (Drummond 2001; Skinner and Aubin 2010).

There has been extensive interest in cigarette cravings in the research of tobacco addiction. Cigarette cravings have been studied in relation to diagnosis, prognostic utility, as an outcome measure, and also as a direct target of interventions. Although cravings were not included in the DSM-IV tobacco addiction criteria, the current version, DSM-V, and an older version DSM-III, listed cravings amongst the criteria for tobacco addiction. A recent review about the clinical significance of drug cravings concluded that cravings have considerable clinical significance across multiple domains and should be routinely included as a clinical outcome in research on treatments for substance-use disorders (Tiffany and Wray 2012). However, the authors also noted that the full potential of cravings remains unknown.

2.2.1 The definition of cigarette cravings

The use of “cravings” to describe an urge in the field of addiction was not always supported. The Expert Committee on Alcohol and The Expert Committee on Mental Health of the World Health Organisation meeting in 1954 criticised the use of “cravings”; they suggested that to avoid confusion, cravings with its everyday connotations should not be used in the scientific literature (Kozlowski and Wilkinson 1987; Word Health Organization 1955). Instead, the use of two terms, physical dependence and physiological dependence was recommended (Word Health Organization 1955). It has been argued that “cravings” refers to a special cases of urges to use drug (a strong desire), and that the use of terms such as “urge” and “disposition” are more suitable (Kozlowski and Wilkinson 1987). However, the use of “craving” or “cravings” in the broader term continued in the field of substance addiction research. For example, authors of the Shiffman-Jarvik Withdrawal Scale (SJWS) considered cigarette cravings to be a continuum, ranging from an aversion to use cigarettes to urges to use cigarettes (Shiffman and Jarvik 1976). Robert West stipulated that the practice of using cravings as a continuum can be justified by the difficulty in determining when desire or needs become cravings (West 1987). Similarly, Kavanagh and colleagues (2005) argued for a continuity model of cravings intensity (Kavanagh et al. 2005). It was proposed that the term “desire” refers to desires for addictive drugs as well as more mundane “wants” (e.g. wanting an ice-cream or wanting to go for a swim), while the term “cravings” refers specifically to drug addictions (Andrade et al. 2009).

One study tried to investigate the meaning of the term cravings among smokers (Kozlowski et al. 1989). They were interested in how smokers and alcoholics perceive the terms “desire” and “cravings”. The authors concluded that the term “urge” should be used instead of cravings. However, the results only showed individual differences in participants’ cravings experience. Similarly, a content analysis of the “cravings term” among 32 smokers highlighted the variability in interpretation of cravings among smokers (Shadel et al. 2001). In addition, smokers seemed to use affective descriptors more often compared to physiology descriptions in this study (Shadel et al. 2001).

Another study investigated the relationship between four semantically different statements about cravings, and an intention to smoke item as measured by The Questionnaire on Smoking Urges (QSU; Kozlowski et al. 1996; Tiffany and Drobes 1991). The following four statements were used: I crave a cigarette right now; I have a desire for a cigarette right now; I do want to smoke now; and I have an urge for cigarette now. All statements were significantly associated with intention to smoke. “Desire” and “want” appeared to be better predictors than “crave” and “urge”. The authors considered a model including “desire”, “want”, and “crave” to be the most appropriate model (Kozlowski et al. 1996).

One of the reasons why there has been a lack of consensus in the definition of cravings is the multifaceted nature of cravings. Cravings are subjective events in time and therefore have an intrinsically high variability.

They can be described on dimensions of duration, frequency as well as their affective intensity (Andrade et al. 2009). Also, the stability of cravings, the distinction between cravings state (e.g. cravings right now) and cravings trait (e.g. cravings over past week) are responsible for the difficulty in describing cravings (Tiffany and Wray 2012). The context in which cravings are considered is also important: the difference between general/tonic and phasic cravings (Tiffany and Wray 2012), abstinence and cue induced-cravings (Perkins 2009), and background and episodic cravings (Shiffman 2000) have been highlighted in the literature. In addition, cravings can be described implicitly (e.g. asking for a cigarette) and explicitly using a "cravings" term (Tiffany and Wray 2012).

In summary, despite cigarette cravings being recognised in the literature and extensively researched, there is no consensus amongst researchers of the definition of cigarette cravings. Most generally, cravings are regarded as a desire or urge to smoke (Sayette et al. 2000). Recently, a systematic review investigating the clinical significance of drug cravings, proposed the following definition: “Cravings are a subjective experience of wanting to use a drug” (Tiffany and Wray 2012). Similarly, cravings were defined as “a subjectively experienced motivational state, which fluctuates over time” (Field et al. 2009b).

2.2.2 The measurement of cigarette cravings

The issues in defining cigarette cravings are also reflected in the development of tools to measure cravings. Numerous questionnaires have been

used in smoking research. Non-verbal measures of cravings, such as reinforcement “proxies”, drug self-administration, psychological responding, neurological responding, cognitive processing and expressive behaviour are often seen only as behaviours associated with self-reported cravings and less central to the measurement of cravings (Sayette et al. 2000). Self-reported measures are routinely used in this field. Single-item measures and multi−item questionnaires are used to assess cigarettes cravings. Often, cigarette cravings measures are included in a withdrawal symptoms questionnaire. Seven commonly used self-reported questionnaires (six withdrawal symptoms measures, and one questionnaire specific to cigarette cravings), and two single-item measures examining cigarette cravings are discussed below. Mood questionnaires that do not specifically link to measures of cigarette cravings are not considered in this section; e.g. Profile of Mood State (POMS; McNair et al. 1992).

The SJWS was developed in 1976 and is probably the oldest published scale measuring tobacco withdrawal (Shiffman and Jarvik 1976). The authors expanded on their previous work and chose 23 items from a 43-item questionnaire. SJWS consists of four subscales: stimulation, cravings, physical symptoms and psychological symptoms. All items are scored on a 1−7 scale (1−very definitely to 7−very definitely not); cravings are assessed using seven items and a combined cravings score is calculated.

The Minnesota Withdrawal Scale (MWS) was developed to test the validity of DSM-III and other symptoms of tobacco withdrawal (see Appendix B **Table 34** for more details; (Hughes and Hatsukami 1986). MWS includes 15 items, is assessed using a five-point scale (0−none, 1−slight, 2−mild, 3−moderate, 4−severe), and is available online (http://www.uvm.edu/~hbpl/?Page=minnesota/default.html; see Appendix B **Table 35** and **Table 36** for more details). Cravings are assessed by one item, desire or cravings to smoke.

The Wisconsin Smoking Withdrawal Scale (WSWS) was developed to ensure mapping with DSM-IV and to allow assessment of different elements of the smoking withdrawal domain (Welsch et al. 1999). WSWS uses four factors, negative affect (with anger, anxiety, sadness and concentration issues subscales), cravings (even though cravings were not part of DSM-IV), hunger, and sleep disturbances. The seven subscales of WSWS relate directly to DSM-IV; two DSM-IV symptoms that are not considered in WSWS are restlessness and heart rate. WSWS is available online (http://www.ctri.wisc.edu/Researchers/researchers_measures&scales.htm; see Appendix B **Table 37** for more details). Cravings are assessed by four items: I have frequent urges to smoke; I have been bothered by the desire to smoke a cigarette; I have thought about smoking a lot; and I have trouble getting cigarettes off my mind, using a five-point scale (0−strongly disagree, 1−disagree, 2−feel neutral, 3−agree, 4−strongly agree).

The Mood And Physical Symptoms Scale (MPSS) assessing cigarette withdrawal symptoms was developed in the 1980s (West and Russell 1988; West et al. 1989; West et al. 1984a; West et al. 1984b; West and Russell 1985). Smokers' irritability, poor concentration, restlessness, depressed mood, hunger, energy, poor sleep at night and feeling physically well were considered in the development of the scale; a five−point scale was used (-2−much less, to 0−some, to +2−much more). Missing a cigarette, difficulty not smoking, awareness of not smoking, pre-occupation with thinking about cigarettes, craving a cigarette, time spent with urges, strength of urges and difficulty of not smoking were considered in the assessment of cigarette cravings (using a six−point scale). Most items in the MPSS reflect withdrawal symptoms as defined in DSM-VI. In addition, cravings were also included in MPSS. In 2004, the scale consisting of five items (irritability, poor concentration, restlessness, depressed mood and hunger) was evaluated (West and Hajek 2004). All items were assessed over the past 24 hours using a five-point scale; 1–not at all, 2–slightly, 3–somewhat, 4–very and 5–extremely. In addition, cravings were assessed using two questions, "How much of the time have you felt the urge to smoke in the past 24 h?" (5–all the time, 4–almost all the time, 3–a lot of the time, 2–some of the time, 1–a little of the time and 0–not at all) and "How strong have the urges been?" (5–all the time, 4–almost all the time, 3–a lot of the time, 2–some of the time, 1–a little of the time and 0–not at all, and 5–extremely strong, 4–very strong, 3–strong, 2–moderate, 1–slight, 0–no urges).

The use of a short (often a single- or two-item measure) instrument assessing cigarette cravings was criticised, and a 32-item QSU was developed

in 1991 (Tiffany and Drobes 1991). Four concepts of cravings were considered in the development; desire to smoke, anticipation of positive outcomes from smoking, anticipation of relief from nicotine withdrawal or from withdrawal-associated negative affect, and intention to smoke. For practical reasons, a short 10-item version of the QSU (QSU-brief; see Appendix B **Table 38** for more details) was then developed (Cox et al. 2001). Two distinct factors were identified during the development; desire and intention to smoke, and anticipation of relief from negative affect. The authors argued that the questionnaire is short enough to allow a quick assessment of cigarette cravings, yet it captures the multidimensional features of cravings (Cox et al. 2001).

Toll and colleagues (2004) re-examined the QSU and proposed a 12-item questionnaire (Toll et al. 2004). A direct comparison with QSU-brief was not possible as the wording of some items in QSU-brief was altered (see Appendix B **Table 39** for more details). However, they identified the same two factors as in QSU-brief. The same research group also re-examined the QSU-brief and proposed a shorter five-item version of the questionnaire (Toll et al. 2006). Again, the same two factors were identified, intention/desire to smoke (assessed by two items: 1. I have a desire for a cigarette right now, and 6. I have an urge for a cigarette), and relief of negative affect or withdrawal (assessed by three items: 4. I could control things better right now if I could smoke, 8. I would do almost anything for a cigarette right now, and 9. Smoking would make me less depressed; items numbered in order they appear in QSU-brief). In addition, Kozlowski and colleagues (1996) also re-examined the QSU and identified three categories of cravings, expectancy, urge and intention.

They suggested that a two- or three-item measure of cravings may yield similar results to a multiple-item measure of cigarette cravings (Kozlowski et al. 1996).

The Tobacco Craving Questionnaire (TCQ) was developed in 2003, and reliability and validity of the instrument was evaluated (Heishman et al. 2003). The TCQ is a 47-item questionnaire with four factors; emotionality, expectancy, compulsivity and purposefulness. A shorter version of the questionnaire was developed in 2008 (Heishman et al. 2008). The short version consists of 12 items and utilises the same four factors as the TCQ (see Appendix B **Table 40** for more details).

The Cigarette Withdrawal Scale (CWS), a 21-item, six-dimension scale, was developed to reflect withdrawal criteria as defined in DSM-IV and ICD-10 (Etter 2005). Six dimensions, cravings, depression-anxiety, irritability-impatience, difficulty concentrating, appetite-weight gain and insomnia were included; each dimension consisted of three or four questions (see Appendix B **Table 41** for more details). Cravings are assessed by three items: The only thing I can think about is smoking a cigarette; I miss cigarettes terribly; and I feel an irresistible need to smoke. In addition, based on qualitative data, an item about a lack of gestures of smoking was added. All items are assessed using five−point scale (0−totally disagree, 1−mostly disagree, 2−more or less agree, 3−mostly agree, 4−totally agree).

Finally, the use of a single-item cravings measure was advised. “Strength of urge to smoke” (assessed using a seven point scale: (Jarvik et al. 2000), and “How much have you craved cigarettes today” (assessed using a six-point scale; (West and Ussher 2010) were proposed as a reliable single-item measures of cigarette cravings.

Review articles discuss the measures assessing tobacco withdrawal. However, usually only a number of commonly used measures are described. In 1996, three scales were reviewed, SJWS, Smoker Complaint Scale (Schneider and Jarvik 1985) and MWS (Patten and Martin 1996). The authors concluded that refining existing, and consideration of other self-reported questionnaires, is needed (Patten and Martin 1996). In 2004, four scales were reviewed, MWS, WSWS, DSM-IV based scale (Shiffman et al. 2000), and SJWS (Shiffman et al. 2004). The authors highlighted that standardisation of a single set of measures in this area is difficult, and suggested that the use of standardised measures may not be required. They concluded that no measure can be recommended in the assessment of tobacco cravings and withdrawal in smoking cessation trials (Shiffman et al. 2004). However, the authors advised the use of a simple readily interpreted measure for cigarette cravings assessment (Shiffman et al. 2004).

In 2007, CWS, MWS, MPSS, SJWS, Smoker Complaint Scale, WSWS, POMS (not assessing cigarette cravings) and Shiffman Scale (SS; Shiffman et al. 1995) were compared and psychometric properties of the scales were discussed (Hughes 2007). This is the only review that reports search strategies

used to identify included studies; however, the results discuss only eight commonly used measures of abstinence effects. The paper does not refer to any recommended reporting guidelines for systematic reviews (Chapter 3, section 1.1.3.1.1 (page 45) describes the use of guidelines in evidence synthesis). The author found that the three brief questionnaires (MWS, MPSS and SS), and the three multi−item questionnaires scores (POMS, SJWS and WSWS) consistently increased with abstinence in prospective studies, and concluded that no measure appeared to be superior (Hughes 2007).

Two studies compared some of the above listed cravings scales directly. One study evaluated a cigarette cravings specific questionnaire (QSU-brief), cigarette cravings measurements as used in four questionnaires of withdrawal (MWS, SS, MPSS, WSWS), and a single item, “How much have you craved cigarettes today” (West and Ussher 2010). The authors concluded that the QSU-brief is no more sensitive than the two-item MPSS cigarette cravings measure, or a single rating of cigarette cravings. Similar results were found in a study evaluating the CWS, WSWS and MWS. The authors concluded that no scale had better properties than any other (Etter and Hughes 2006).

In addition, validated questionnaires are often modified to suit the requirements of researchers. Both the composite scores and the individual scores of the questionnaire subscales have been reported and utilised by authors. Sometimes even the individual items within a questionnaire are of interest to the researchers. Finally, a systematic review according to a

COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist (www.cosmin.nl; Mokkink et al. 2009), identifying all available questionnaires measuring cigarette cravings, and assessing the measurement properties of the instruments aiming to measure cigarette cravings in smokers has not been conducted.

In summary, cigarette cravings are considered an important outcome relating to smoking cessation and although there are many limitations to self-reported measures, self-reports of cravings are seen as the gold standard for assessments of cigarette cravings. However, no specific measurement tools are recommended for the measurement of cigarette cravings. Short measures of cravings, although critiqued, appear to be adequate in measuring cigarette cravings. The measurement properties of cigarette cravings, such as psychometric properties, reproducibility, validity and responsiveness, remain to be systematically evaluated. In addition, the psychometric characteristics of craving assessments should be established under the conditions and groups of individuals for which the assessment is to be used (Tiffany and Wray 2012).

2.2.3 Cue-reactivity and attentional bias

Many theoretical models posit that substance-related stimuli (cues) will capture the attention of people who use addictive substances (Hogarth et al. 2010). In the classical conditioning model, attention grabbing properties of smoking stimuli indicate the incentive salience of these cues and would demand

a smoker's interest in the drug (Robinson and Berridge 1993). Substance users tend to use drugs or relapse more in the presence of stimuli associated with drug use. For example, environmental cues can trigger strong cigarette cravings, even long after the acute effects of nicotine withdrawal have subsided (Carter and Tiffany 1999).

Smoking cue-induced cravings (also described as phasic cravings, cue induced-cravings or episodic in the literature) have been successfully manipulated in many experimental studies. Cue reactivity was measured by (i) self-reports of cravings; (ii) self-reports of mood; (iii) physiological responses (such as heart rate, skin conductance or temperature); (iv) specific drug-use behaviour (such as number of cigarette puffs, delay in onset of cigarette smoking or speed of smoking); (v) regional brain activation (e.g. measured by fMRI); and (vi) attentional bias towards smoking stimuli (e.g. Carter and Tiffany 2001; Droungas et al. 1995; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2012; Payne et al. 1996; Taylor and Katomeri 2007; Tiffany et al. 2000; Warren and McDonough 1999; Waters and Feyerabend 2000).

Cigarette cue reactivity is associated only with modest changes in physiological measures, suggesting that cigarette cravings are appropriate for evaluation of cue manipulations (Carter and Tiffany 1999). Attentional bias is considered to either cause or indicate the underlying processes that cause substance seeking behaviour (Field et al. 2009a). A systematic review concluded that cravings and attentional bias have reciprocal properties;

cigarette cravings cause attentional bias, and an attentional focus to smoking cues further increases cigarette cravings (Field and Cox 2008). However, the exact relationship between cravings and attentional bias remains undiscovered (Field et al. 2009a). A review investigating the relationship between cue-induced cravings and treatment outcome found a weak significant association between cravings in response to smoking related cues and sub-sequent smoking in three studies (Wray et al. 2013).

Attentional bias can be assessed by using proxy methods such as reaction time in a cognitive task, or directly with eye-tracking. The modified Stroop task (Cox et al. 2006), and the pictorial dot probe task (Mogg and Bradley 2002) are commonly used in drug related studies (Oliver and Drobes 2012). By comparing a reaction time on trials where participants respond to smoking related stimuli with trials following neutral stimuli, inferences about attentional bias can be made. However, the two cognitive tasks are different, the former assesses competition for processing resources between perceptual and semantic features of stimulus (presented within the central focus of attention), whereas the latter assesses the spatial allocation of visual attention (Mogg and Bradley 2002). Thus, the pictorial version of the visual probe task may be a better indicator of the direction of smokers' attention. However, the reliability of the pictorial dot probe task has also been criticised (Ataya et al. 2012; Schmukle 2005). Overall, eye-tracking, a direct measure of attentional bias, is the preferred method (compared with cognitive tasks) in attentional bias assessment (Field and Christiansen 2012). Eye-tracking offers a more precise measure of attentional bias, and also allows investigation of two dimensions of

attentional bias; delayed disengagement of attention (by duration of eye fixation on smoking stimuli), and initial orienting of attention (by initial shift in attention; Field et al. 2009a).

In summary, self-reported measures of cigarette cravings are appropriate for evaluation of cue manipulations (Carter and Tiffany 1999). Although it was suggested that no relationship between cue-induced cravings and smoking outcomes exists (Perkins 2009), evidence of a weak relationship has been reported (Wray et al. 2013). An attentional focus to smoking cues further increases cigarette cravings (Field and Cox 2008) and the preferred method of measuring attentional bias is eye-tracking (Field and Christiansen 2012; Field et al. 2009a).

2.3 Summary and Implications

Cigarette cravings have a clinical significance in tobacco research and are a recommended clinical outcome in smoking cessation studies. Yet, the role of cigarette cravings in tobacco addiction is still not fully understood, and therefore the mechanisms behind the effects of PA on cigarette cravings are unknown. Questions like “What exercise is more effective?” and “Who benefits most?” have not been answered yet. However, no measurement tool has been recommended for cigarette cravings assessment. Most craving assessments focus on strength of cravings, while other cravings dynamics, such as frequency or duration (time spent with cravings), are less common. Self-reported methods are considered to be the gold standard. In addition, both single-item cigarette cravings, and multi-item cigarette cravings methods have been used. Cigarette cravings are frequently measured as a part of withdrawal symptoms questionnaires. Specifically, MPSS, a withdrawal symptoms questionnaire including an item “How strong have the urges been?”, and QSU, a multi-item cigarette cravings questionnaire including an item “I have a desire for a cigarette right now”, are commonly used and often modified in acute studies assessing cigarette cravings.

In summary, measures relating to “strength of cravings” will be the focus of this thesis. Two generally used single-item cigarette cravings measures from two common cravings assessment tools, MPSS and QSU, will be utilised: “How strong have the urges been (SoD)?” and “I have a desire for a cigarette right now (DtS)”. In addition, the stability of cravings will be considered. Chapters 4–6

(Studies 1–3) assessed the state levels of cravings (cravings right now), while Chapter 7 (Study 4) examined the effects of habitual PA on cigarette cravings assessed over the last week. Finally, the effects of PA on attentional bias to smoking cues using both reaction time and eye-tracking technology, and withdrawal symptoms (MPSS) are examined.

Chapter 3: Research Design

This chapter describes the design adopted by this research to achieve the aims and objectives stated in Chapter 1. Specifically, the first section of this chapter discusses the role of evidence synthesis in research, its methodology and highlights the strength and weakness of a systematic approach to evidence synthesis. The second section summarises the choice of research design adopted in this research.

3.1 Evidence synthesis

Results of an individual and often small-scale study offer only limited evidence. The volume of data that needs to be considered by researchers and policy makers is constantly expanding; it has become increasingly difficult and time-consuming for an individual to read and critically evaluate all available evidence in a specific field of interest (Egger et al. 2001). Systematic reviews and meta-analyses systematically and critically summarise findings. In addition, evidence synthesis is needed to identify gaps in research and formulate research questions (The Cochrane Collaboration 2011).

Traditionally, reviews were written in a narrative style by experts in a specific research area. Reviews were often published in medical journals and usually described the epidemiology, diagnosis, treatment and likely outcomes of

a specific condition (Deeks 1998). The traditional review format was subjective and prone to bias. Such limitations were soon recognised and the need for scientific methods to identify, assess, and synthesise information was acknowledged (Mulrow 1987). Professor Archibald Lemane Cochrane, after whom The Cochrane Collaboration was named, was among the first to recognise and promote the role of systematic reviews in evidence synthesis in health care (Levin 2001). In the UK, The National Institute for Health Research (NIHR) is a global leader in producing and promoting evidence synthesis. NIHR supports three systematic review programmes: UK Cochrane Centre and Collaboration review group, Centre for Reviews and Dissemination (CRD), and Technology Assessment Reviews (www.nihr.ac.uk).

3.1.1 Systematic Reviews

Systematic reviews allow for objective and transparent appraisal of evidence (Egger et al. 2001). They involve comprehensive systematic literature searches, with pre-defined methods, and explicit reporting. With the introduction of systematic reviews, the need for guidelines has emerged (Deeks 1998). The Quality of Reporting of Meta-analyses (QUOROM) statement was published in 1999 (Moher et al. 1999). The Meta-analyses of Observational Studies in Epidemiology (MOOSE) recommendations were published a year later (Stroup et al. 2000). Systematic reviews also highlighted the need for rigorous reporting of primary studies, and the CONsolidated Standards of Reporting Trials (CONSORT) statement, a recommendation for improving the quality of reports of parallel-group randomised trials was published in 2001 (Moher et al. 2001).

Systematic reviews have become essential tools in maintaining current knowledge of accumulating evidence and are a regular feature of many journals. There are about 2500 new systematic reviews published every year (Moher et al. 2007). However, the quality of reporting has been found to be inconsistent (Moher et al. 2007). The lack of rigorous reporting resulted in updating the QUOROM statement, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was published in 2009 (Liberati et al. 2009; Moher et al. 2009). Tools like the PRISMA checklist and PRISMA flow diagram were developed to increase quality of systematic reviews and are available to researchers online (http://www.prisma-statement.org/statement.htm). Similarly, the CONSORT statement was updated in 2010 (Schulz et al. 2010). In addition, a dedicated CONSORT website is available to researchers (http://www.consort-statement.org/). Importantly, an international initiative The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network, seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines; the EQUATOR website lists all key reporting guidelines (http://www.equator-network.org/). In addition, The Cochrane Collaboration Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org/) and The Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) provide online available guidelines for conducting and evaluating systematic reviews.

3.1.2 Meta-analysis

Meta-analyses use statistical methods to combine the results of individual studies and allow synthesis of numerical results and if appropriate will enhance the precision of estimates of treatment effects (The Cochrane Collaboration 2011). Methods to pool results from individual studies are not new; in 1894 statistician Karl Pearson, was probably the first to report the use of formal techniques in combining data from different samples (Egger and Smith 1997). Yet, the first meta-analysis assessing the effect of a therapeutic intervention was published in 1955 (Beecher 1955). Meta-analyses traditionally combine aggregate results (usually obtained from a published study), and are an integral part of evidence-based research (Riley et al. 2011). Meta-analyses can be used to combine evidence from randomised controlled trials, and evidence from observational studies. The Cochrane Collaboration Handbook for Systematic Reviews suggests that meta-analyses increase statistical power and may be able to answer questions not posed by the individual studies or settle controversies arising from the individual studies. However, it also recognises the need for careful consideration before pooling results from primary studies. Meta-analyses do not guarantee improved results, they are tools in evidence synthesis and need to be used appropriately (The Cochrane Collaboration 2011).

Meta-analysis methods have been criticised, for example, for inappropriately combining data from dissimilar primary studies, resulting in a summary effect that will not take into account possible important differences

across studies (Borenstein et al. 2009). However, it has been well argued that the same issues that apply to meta-analyses also apply to narrative reviews. The key advantage of a systematic approach is that all steps are clearly described and transparent (Borenstein et al. 2009). Nevertheless, the research question, and the design and possible biases of the individual studies, need to be carefully examined before deciding whether meta-analysis is a suitable form of summarising evidence. Importantly, standardised reporting is needed (The Cochrane Collaboration 2011).

Fixed effect and random effects meta-analyses

Meta-analyses do not simply average results across studies. The results of individual studies are weighted and combined. Some studies have less uncertainty than others, for example, large trials provide more precise results (smaller variance associated with point estimate), compared with small trials. The two main methods of combining numerical evidence are fixed effect and random effects meta-analysis. Fixed effect meta-analysis methods assume that individual studies are estimating the same underlying treatment effect; the true underlying effect size is common for all studies, and the pooled (summary) effect is the estimate of the common effect size. Random effects methods assume that different studies are estimating different but related effect sizes. Random effects analyses assume a distribution of treatment effects across studies (each study can have a different treatment effect), and the pooled estimate represents the estimate of the mean treatment effect common across all studies (Borenstein et al. 2009; Riley et al. 2011; Sutton et al. 1998; The

Cochrane Collaboration 2011). Fixed effect models give each study a weight directly proportional to its precision; e.g. using the inverse variance method the weights are an inverse variance of the study's effect estimate. Similarly, random effects models also adjust the study weights for the study specific variance, and in addition they incorporate an adjustment for between-studies heterogeneity (tau-squared; Riley et al. 2011; Sutton et al. 1998; The Cochrane Collaboration 2011).

3.1.3 Individual Participant Data Meta-Analyses

Individual participant data (IPD) meta-analyses are considered to be the gold standard (Stewart & Tierney, 2002). IPD meta-analyses use the original data for each participant in each study. Authors of the primary studies need to be approached and the raw IPD are obtained and collated. Therefore, IPD meta-analyses require collaboration among researchers and may be very time-consuming, although authors' cooperation may help with the identification of eligible studies (Clarke 2005; The Cochrane Collaboration 2011) and support collaboration on future research (Stewart and Tierney 2002). IPD analyses can present the most reliable means of combining data from randomised controlled trials (Lyman and Kuderer 2005; Riley et al. 2011; Stewart and Clarke 1995). One of the benefits of IPD meta-analyses is the ability to perform subgroup analyses. Subgroup analyses may be needed to discriminate between participants who do and do not benefit from a particular treatment and allow a thorough assessment of effect modifiers (The Cochrane Collaboration 2011). IPD meta-analyses are specifically recommended for repeated measures data

(van Walraven 2010). In addition, IPD meta-analyses may be beneficial when many studies are either unpublished or published only in the 'grey literature' (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 (The Cochrane Collaboration 2011).

There are some disadvantages to conducting IPD meta-analyses. Collating the data is by far the most challenging and time-consuming aspect. Also, handling and cleaning the raw data while keeping communication lines with primary authors open can be challenging (Clarke 2005; van Walraven 2010). The balance between time and resources, and the quality of the analyses, is the deciding factor when determining whether to use IPD or aggregate analyses (Clarke 2005).

One-stage and two-stage models for individual participant data meta-analyses

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, is derived for each primary study and then combined 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 (Simmonds et al. 2005). Of the two basic approaches to meta-analyses, the 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 (Lambert et al. 2002). 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.

3.1.4 Heterogeneity and risk of bias

Statistical heterogeneity is the variability in the intervention effects in the different studies, and it is the consequence of clinical and methodological variability. Clinical heterogeneity refers to the variability in participants, interventions and outcomes studied in the individual studies, whereas methodological heterogeneity relates to variability due to differences in study design and the variability in risk of bias across the studies. However, statistical heterogeneity may exist even if the primary studies indicate the same direction of the treatment effects (such as all the studies estimating a beneficial effect of treatment). In this case the magnitude, rather than the direction, of the effect sizes may be the source of heterogeneity (Sutton et al. 1998).

Although meta-analyses may reduce statistical imprecision and may help to indicate a risk of publication bias by visual inspection of funnel plots and the use of statistical tests (Sutton et al. 1998; The Cochrane Collaboration 2011), it cannot prevent the inappropriate combination of data from dissimilar primary studies. If statistical heterogeneity between primary studies is found, the

potential sources (clinical or methodological) of such heterogeneity require investigation. Meta-analyses should be only be considered among studies that are sufficiently homogenous and allow for meaningful summary of the results of the primary studies; therefore, heterogeneity among primary studies should be investigated (The Cochrane Collaboration 2011).

The most common test of heterogeneity is the Q statistic and also graphical informal tests (Sutton et al. 1998). Statistically significant values for the Q statistic may indicate the presence of heterogeneity, while non-significant results are not evidence of homogeneity. Some limitations of the Q statistic were recognised and I^2 methods were recommended to be used in combination with Q statistics (Higgins and Thompson 2002). The I^2 statistics represents the proportion of the total variability in the study point estimates that can be attributed to between-studies heterogeneity and not to within-study error. The Q statistic and I^2 methods are related ($I^2 = [(Q-df)/Q]*100\%$; where df are degrees of freedom of the Q statistics) and both methods are endorsed in the Cochrane handbook (The Cochrane Collaboration 2011).

The issues of publication bias and reporting bias are well acknowledged (Dwan et al. 2008; The Cochrane Collaboration 2011). On average, published trials showed a 9% larger intervention effect than grey literature trials (Hopewell et al. 2007). Including data from grey literature would be an obvious way of solving this problem. However, unpublished studies may be of lower

methodological quality than published studies and may also introduce bias into the review (The Cochrane Collaboration 2011).

3.2 Summary and Implications

Meta-analysis is not a necessary feature of a systematic review, and in some scenarios may be inappropriate. Meta-analysis is often used to quantitatively combine data identified by a systematic review, including unpublished and `grey' literature. Fixed effect meta-analysis is most suitable when there is little between-studies heterogeneity, while random effects meta-analysis is more suitable where there is some heterogeneity present. IPD meta-analyses, although time consuming, offer many benefits over traditional aggregate meta-analyses and are considered to be the gold standard in evidence synthesis. IPD meta-analyses may reduce statistical imprecision and may help with bias clarification and IPD meta-analyses using data from randomised controlled trials are considered to be the best source of clinical effectiveness evidence.

In summary, a systematic review of literature will identify randomised controlled trials to quantify, using IPD, the effects of short bouts of PA on cigarette cravings among temporarily abstaining smokers (Study 2: "The acute effects of physical activity on cigarette cravings: Systematic review and individual participant data meta-analysis"). Additional analyses of the acquired IPD will be used to identify the demographic and smoking characteristics of smokers who may benefit to a greater or lesser extent from PA, whether changes in affect mediate these effects, and if any attributes of PA are associated with cigarette cravings among temporarily abstaining smokers (Study 3: "The acute effects of physical activity on cigarette cravings:

Exploration of potential moderators, mediators and physical activity attributes using systematic review and individual participant data meta-analyses"). In addition, a search of grey literature will be conducted. Individual participants' data will be requested from authors of included primary studies and heterogeneity and publication bias will be investigated. The use of fixed and random effect(s) meta-analyses will be considered, and the one-stage and the two-stage models will be applied as appropriate.

Chapter 4: The effects of brisk walking and seated isometric exercise on cigarette cravings and attentional bias to smoking cues

4.1 Introduction

Evidence suggests that short bouts of physical activity (PA) can reduce self-reported cravings and withdrawal symptoms (Taylor et al. 2007). Taylor and colleagues (2007) identified 12 studies comparing a bout of PA with a passive condition, and two studies that compared two intensities of exercise. All studies reported positive effects of PA on cigarette cravings and withdrawal symptoms, and no difference was found for different PA intensities (Taylor et al. 2007).

Since 2007, acute effects of PA on cigarette cravings were quantified in a meta-analysis (Roberts et al. 2012) and in a meta-analysis using individual patient data (IPD; Haasova et al. 2013). In addition, another IPD meta-analysis identified that the intensity of PA is the most important attribute of PA associated with cigarette cravings (Haasova et al. 2014). However, before the data from these meta-analyses (Haasova et al. 2013; 2014; Roberts et al. 2012) were available, only one study directly compared the effects of different types of PA (Elibero et al. 2011). In this study, hatha yoga and walking were found to decrease cigarette cravings compared with a passive control condition, while no difference was found between the two PA conditions (Elibero et al. 2011).

Aerobic exercise, e.g. walking (Faulkner et al. 2010; Janse Van Rensburg and Taylor 2008; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005) was repeatedly found to decrease cigarette cravings. However, it was suggested that aerobic exercise may not be a practical strategy in some situations, e.g. in a workplace (Ussher et al. 2006).

Attentional bias (AB) for substance-related stimuli is associated with substance use disorders (Field et al. 2014). AB is considered to either cause or indicate the underlying processes that cause substance seeking behaviour (Field et al. 2009a). AB can be assessed by using proxy methods such as reaction time in a cognitive task, or directly with eye-tracking; the preferred method of measuring attentional bias is eye-tracking (Field and Christiansen 2012; Field et al. 2009a). AB operates in two different attentional processes, fast automatic initial shifts in attention and maintained attention (Field and Cox 2008); initial AB can be defined as the direction of the initial shift of gaze, and maintenance AB as the duration of gaze.

Using the eye-tracking methodology, Field and colleagues (2004) found that deprived smokers maintained their gaze for longer on smoking related images in a pictorial probe task (compared with control cues), relative to when non-deprived; a significant effect of picture type and deprivation condition interaction on maintenance AB was found (Field et al. 2004). Similarly, the eye-tracking technology identified differences between smokers with low and high nicotine dependence (Mogg and Bradley 2002), and between smokers and non-

smokers (Bradley et al. 2007; Mogg et al. 2003). Janse Van Rensburg and colleagues (2009) found that 15 minutes of moderate intensity cycling had significant effects on both dimensions of AB: maintenance (measured by percentage of dwell time), and initial AB (measured by percentage of direction of first fixation; Janse Van Rensburg et al. 2009a). The authors concluded that further studies may wish to include alternative measures of AB and postulated that a short bout of isometric (ISO) exercise may have similar effects on AB as 15 minutes of moderate intensity cycling (Janse Van Rensburg et al. 2009a).

The purpose of the current study was to extend the research into the effects of acute PA among temporarily abstaining smokers. The primary aim of this study was to directly compare the effects of two types of PA, walking and ISO exercise (compared with a passive control condition) on cigarette cravings and withdrawal symptoms in temporarily abstaining smokers. In addition, a secondary aim of this study was to examine the effects of PA and AB in temporarily abstaining smokers. A three-arm cross-over randomised study compared two 10-minute PA interventions; brisk walking and seated ISO exercise, with a rest control condition. This is the first study directly comparing the effects of ISO exercise and walking on cigarette cravings and withdrawal. In summary, the research questions explored in this chapter are:

- What are the effects of 10 minutes of walking, and 10 minutes of ISO exercise, compared with a control condition, on cigarettes cravings, withdrawal and AB in temporarily abstaining smokers?

- Are there any differences in the effects of these PA interventions on cigarette cravings, and/or withdrawal symptoms, and/or AB in temporarily abstaining smokers?

4.2 Methods

The study received institutional ethical approval and all participants gave their informed consent. Smokers were recruited using posters, flyers, the University of Exeter newsletter, and from the Exeter 10000 database (http://clahrc-peninsula.nihr.ac.uk/news/120-opportunity-to-take-part-in-clinical-research--exeter-10-000-study.php). Participants were asked to abstain from smoking for a minimum of 3 hours prior to attending to participate in the study. Upon arrival in the laboratory, smoking abstinence was confirmed by a Bedfont Smokerlyzer (CO level < 10 parts per million). The study used a randomised cross-over design with the order of the three intervention conditions randomly assigned, participants attended one session (of an approximate duration of 45-60 minutes) on each of three consecutive days (three sessions in total); brisk walking and seated ISO exercise were compared with a rest control condition (**Figure 2**).

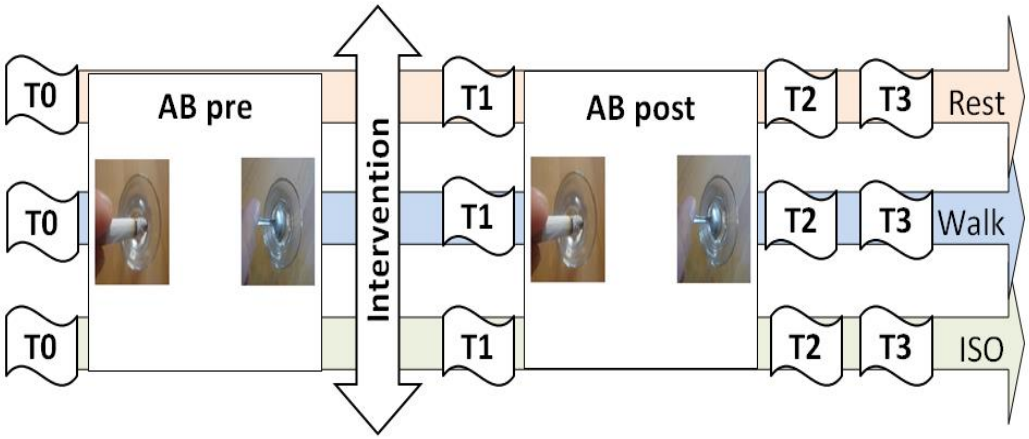


Figure 2 Study design
Notes: T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2; AB pre = attentional bias measurement during a probe task before intervention; AB post = attentional bias measurement during a probe task after intervention; ISO = isometric exercise condition; Walk = walking condition; Rest = control condition.

Cravings and withdrawal baseline measurements were measured at time T0. Next, partcipants undertook the baseline probe task (AB pre). The interventions (walking and ISO exercise) followed immediately after the probe task. Post-intervention cravings and withdrawal measures were taken at time T1 (imediatelly after the intervention finished), at time T2, which was immediately after the second probe task (AB post), and at time T3 (5 minutes after time T2; **Figure 2**).

All baseline AB measures were collected during the baseline probe task (AB pre), with the interventions (walking, ISO exercise) following immediately after the task. Post intervention AB measurements were taken during the second probe task (AB post) immediately after the intervention took place (**Figure 2**).

4.2.1 Participants

Participants were eligible if they had been smoking for at least 2 years, smoked 10 or more cigarettes per day, were aged between 18 and 50 years, had no health issues which prevent them from exercising at a moderate intensity, were not attempting to quit smoking and were willing to abstain from smoking for at least 3 hours prior to each of the three visits. Participants were reimbursed up to £20 for travelling expenses.

4.2.2 Interventions

In the rest condition, participants were instructed to listen to a text recording while sitting on a chair (Ussher et al. 2009; Ussher et al. 2006). Participants were left alone for the whole duration of the recording (10 minutes).

In the walking condition, the treadmill was set to an incline of 1% to simulate a more natural environment (Jones and Doust 1996). After a brief period of familiarisation involving a 2-minute warm-up, participants self-selected a suitable walking speed to represent a moderate intensity exercise; at a subjective rating of perceived exertion of 11–13 (RPE, 6-20 scale; Borg 1998). Participants were instructed to walk briskly as if 'late for an appointment' or at a pace of 'one trying to catch a bus', but not to be 'out of breath' for 10 minutes, followed with a 1-minute cool-down (Taylor and Katomeri 2007; Taylor et al. 2005). A heart monitor (POLAR) was worn during the session to measure relative exercise intensity (expressed as percentage of heart rate reserve) and the participants' RPE scores were recorded. In addition, change in affect following exercise was measured using Feeling Scale (FS; Hardy and Rejeski 1989) and Felt Arousal Scale (FAS; Svebak and Murgatroyd 1985); FS is assessed on a -5 to +5 Likert scale, and FAS is assessed on a 1–6 Likert scale. Contact with the participants was kept to a minimum.

In the ISO exercise condition, participants sat on a chair while listening to the instruction recording (Ussher et al. 2009; Ussher et al. 2006). Prior to the recording, during a brief period of familiarisation (2 minutes) participants were

introduced to six ISO exercises (clench the jaw, open and close fists, push the palms of the hand against each other, push down on top of the thighs, squeeze the inner thighs and press the soles of the feet down). Participants were also provided with a picture of the exercises (Appendix D **Figure 26**). Similarly to the rest condition, participants were left alone to perform the exercises as instructed by the recording (10 minutes).

4.2.3 Procedures

Cigarette dependence was measured using the Fagerström Test of Cigarette Dependence (FTCD; Fagerström 1978; 2012; Heatherton et al. 1991). The Seven Day Recall Physical Activity Questionnaire (Blair et al. 1985) was used to record light, moderate and vigorous intensity PA over the past week; moderate and vigorous intensity PA were combined into moderate and vigorous intensity physical activity (MVPA).

Dot probe task

The dot probe task was programmed using the E-prime version 1.2 (Psychology Software Tools, Inc). Pairs of images were presented on a 14-inch monitor; the images were sized to 8 cm wide by 8 cm high and were presented 8 cm apart. Participants sat 65 cm away from the screen. Before the onset of each pair of images a cross appeared in the middle on the computer screen for 500 milliseconds (to make sure that the participant's attention was in the middle of the screen before the onset of the pictures). This was followed by a 2000-

millisecond long display of images (Mogg et al. 2003; Mogg et al. 2005). Then both pictures disappeared and one of the pictures (left or right) was replaced with a dot (probe). The probe was displayed for up to 2000 milliseconds, or until the participant indicated the probe position by striking a selected key on a keyboard (**Figure 3**). Participants were required to look at the cross and strike a key as quickly as possible to indicate the probe location. To maximise consistency, all participants were presented with written instructions. All participants received 16 practice trials using a combination of neutral images at their first visit.

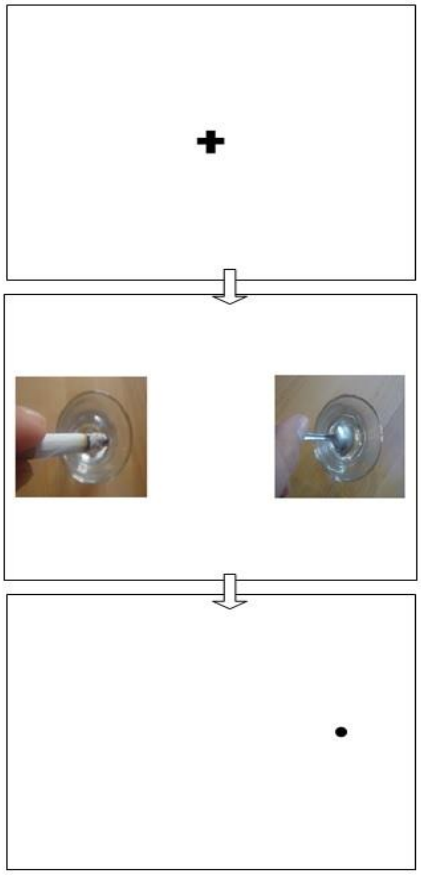


Figure 3 Dot Probe task

Notes: Cross appeared for 500 milliseconds, followed with a 2000 milliseconds long display of a pair of images, then a probe (left or right location) probe is displayed for up to 2000 milliseconds, or until the participant indicated the probe position.

The dot probe task included 32 critical trials of smoking related and neutral images, 16 filler trials (pairs of neutral images) and 2 buffer trials (pairs of neutral images at the beginning of the task). All trial combinations in the experiment occurred in a random sequence and all smoking images appeared equally on the left and right of the screen, as did the probe. Images used in the practice and buffer trials were different from the neutral images used in the critical and filler trials.

Eye-tracking

The Applied Science Laboratories (ASL) Mobile Eye eye-tracker (**Figure 4**) recorded gaze position using a camera located in the eye-tracking glasses. The eye-tracking equipment was calibrated before each trial using a 2x3 dot array; participants were instructed to follow the array dots with their eyes. The calibration procedure was repeated before and after each probe task. The ASL Mobile Eye measures the position of the participant's gaze every 40 milliseconds (25Hz); therefore a fixation was defined as having a minimum duration of 80 milliseconds (2*40 milliseconds).

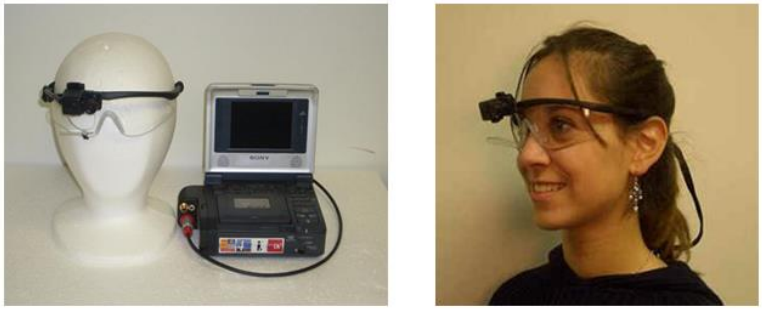


Figure 4 The Applied Science Laboratories Mobile Eye eye-tracker

4.2.4 Cigarette cravings and withdrawal measures

Withdrawal symptoms were assessed using the Mood and Physical Symptoms Scale (MPSS; West and Hajek 2004; West and Russell 1985) consisting of six items; irritability, poor concentration, restlessness, depressed mood and hunger. All items were assessed using a five point Likert scale (1 = not at all, 2 = slightly, 3 = somewhat, 4 = very and 5 = extremely). Two single-item cigarette cravings measures using a seven point Likert scale were included; Desire to Smoke (DtS; Tiffany and Drobes 1991) and Strength of Desire to Smoke (SoD; West and Hajek 2004; West et al. 1989; West and Russell 1985). SoD is assessed using the statement 'How strong is your desire to smoke right now?' (1 = very weak, 4 = neither strong or weak, 7 = very strong), and DtS is assessed using the statement 'I have a desire for a cigarette right now' (1 = strongly disagree, 4 = neither agree or disagree, 7 = strongly agree).

4.2.5 Attentional bias

Two dimensions of AB were assessed directly using the eye-tracking data. The initial AB was expressed as the percentage of first fixation to smoking images in relation to neutral images in critical trials (Field et al. 2004; Janse Van Rensburg et al. 2009a), and maintenance AB was expressed as the percentage of dwell time (expressed as the sum of individual fixations) spent on smoking images in relation to neutral images, in critical trials (Janse Van Rensburg et al. 2009a). All eye-tracking data were analysed using the Quiet Eye Solution

software. Only valid critical trials, when the participant fixated his/her gaze on the cross before critical trial onset for a minimum of one fixation duration, were analysed (Field et al. 2004; Janse Van Rensburg et al. 2009a). In addition, only fixations that occurred at least 120 milliseconds after the critical trial's onset, and at least 120 milliseconds before the picture offset, were analysed.

Secondly, AB was expressed as an AB reaction time score using the result from the dot probe task. The mean reaction time to salient cues (smoking images) was subtracted from the mean reaction time to neutral images (e.g. Ehrman et al. 2002; Mogg and Bradley 2002). Positive bias scores reflect faster reaction time in detecting probes behind salient images and indicate AB towards smoking images. Only critical trials were analysed. Trials with errors (when participants indicated a wrong probe position, or missed a trial and did not indicate any key) and trials with reaction time less than 200 milliseconds or greater than 1000 in critical trials were excluded from the analyses (Ehrman et al. 2002; Townshend and Duka 2001). Values less than 200 milliseconds may indicate that the response was initiated before the onset of the target. Reaction times longer than 1000 milliseconds may suggest inattention to the task or a motor error (Ehrman et al. 2002).

4.2.6 Power calculation

G*Power3 was used for power analysis (http://www.gpower.hhu.de/en.html; Faul et al. 2007). The power calculations in the current study were based on a study which shared a similar rationale and

study design (Janse Van Rensburg et al. 2009a). All power calculations were based on the assumption that the correlation between repeated measures (time) is 0.75 and sphericity was assumed. The alpha level was set at 0.05 and power (1-beta) at 0.80 a priori. For simplicity, a parallel design was assumed for the three treatment conditions. Using a two-factor design, with three conditions by two time points, 18 participants were needed to detect an effect size eta^2 of 0.416 in the percentage of dwell time, and 21 participants were needed to detect an effect size eta^2 of 0.343 in the percentage of first fixation.

In addition, based on the effect size reported in the Taylor and colleagues (2007) review, it was expected that a sample size of 21 would yield power of 99.7% to detect the effects of PA on cigarette cravings using a two-factor design, with three conditions by four time points (Taylor et al. 2007). Similarly, based on a study by Ussher and colleagues (2006), it was expected that a sample size of 21 would yield power of 80.6% to detect the effects of PA on withdrawal symptoms using a two-factor design, with three conditions by four time points (Ussher et al. 2006).

4.2.7 Statistical analyses

Continuous data were described using the mean and standard deviation (SD) and the median and interquartile range (IQR). Categorical data were described using proportions. Linear mixed regression models with restricted maximum likelihood approach were used to identify the effects of walking and ISO exercise on cravings and withdrawal; main effect of time, main effect of

treatment and time/treatment interaction. Allowing for a cross-over data design used in this study, a random intercept on participant (to allow adjustment for multiple observations on individual participants) was used in the analyses (Brown and Prescott 1999). The regression coefficients represent the mean difference between the two PA interventions compared to the control condition. For example, a mean difference of -0.5 would indicate that cravings were 0.5 points lower (using the 1–7 Likert cravings scale) in the intervention group compared with the control group. Similarly, a mean difference of 0.5 would indicate that withdrawal was 0.5 point higher (using the 1–5 Likert MPSS scale) in the intervention group compared with the control group.

Post hoc tests included the global Wald test for the effects of time, treatment and the time/treatment interaction. If appropriate, the effect of the two treatments compared with control condition was investigated using contrast effects at each time point. Sensitivity analyses for cigarette cravings and withdrawal data included linear mixed models using only one post treatment measurement (T1); T2 measurement (taken immediately after the second probe task; AB post) and T3 measurement (taken 5 minutes after time T2) were omitted from the analyses. In addition, sensitivity analyses for all outcomes included analyses where the two treatment conditions (walking and ISO exercise) were combined into one PA condition and included in the linear mixed models analyses. In addition, the associations between cigarette cravings and AB post intervention (T1) were assessed using Spearman correlations (Janse Van Rensburg et al. 2009a). All statistical analyses were performed using Stata 13 and the significance threshold was set at 0.05 in all analyses.

4.3 Results

4.3.1 Participants

Twenty six participants were screened for study inclusion;20 participants (13 male; 65%) were recruited. Bedfont Smokerlyzer confirmed temporary abstinence (<10 parts per million); mean (SD) CO level was 4.3 (2.5), 4.7 (2.2) and 4.6 (2.4) parts per million in the rest, exercise and control conditions respectively. **Table 2** describes the participants' demographics.

Table 2 Participant characteristics; demographic and background variables

Characteristics	**Descriptives** Mean (SD)	Median (IQR)
Age (years)	30.90 (0.49)	29.00 (22.50, 38.50)
BMI (kg/m^2)	25.01 (4.25)	24.73 (22.00, 27.00)
FTCD	3.53 (2.04)	4.00 (2.00, 4.00)
Cigarettes per day	14.58 (3.42)	15.00 (13.00, 15.00)
Time spent smoking (years)	12.53 (10.11)	8.00 (5.00, 20.00)
MVPA (min per day	44.44 (32.38)	38.57 (22.86, 57.86)

Notes: BMI = body mass index; FTCD = Fagerström Test for Cigarette Dependence; N = Number of participants; SD = standard deviation; IQR = inter-quartile range; MVPA = moderate and vigorous intensity physical activity.

In the walking condition, participants walked at a mean (SD) heart rate of 105.37 (14.06) beats per minute, equivalent to a mean 86.8 (SD 13.8) percentage points of heart rate reserve, and rated their subjective exercise intensity (RPE) at a mean (SD) of 11.74 (0.81). A mean (SD) increase in FS of 0.58 (0.95) and in FAS of 0.02 (0.82) was recorded. **Table 3** describes baseline measures in each of the three conditions.

Table 3 Participant characteristics; baseline measures by condition

Outcomes	Rest condition Mean (SD)	Walking condition Mean (SD)	Isometric exercise condition Mean (SD)
Strength of Desire	4.45 (1.73)	4.80 (1.67)	4.35 (1.84)
Desire to Smoke	4.55 (1.88)	4.75 (1.80)	4.60 (2.11)
MPSS	1.83 (0.63)	1.72 (0.44)	1.69 (0.44)
Difficulty concentrating	2.05 (0.94)	2.2 (0.85)	2.40 (0.88)
Depression	1.25 (0.44)	1.10 (0.31)	1.15 (0.37)
Irritability	1.70 (0.89)	1.80 (0.70)	1.75 (0.79)
Restlessness	2.05 (0.63)	1.72 (0.44)	1.69 (0.44)
Hunger	2.10 (1.12)	2.05 (1.00)	1.80 (1.01)
Reaction Time Attentional Bias Score	16.50 (45.67)	17.26 (48.28)	14.97 (52.77)
Percentage of dwell time	43.86 (8.66)	45.51 (7.13)	43.27 (8.30)
Percentage of first fixation	55.17 (11.86)	51.12 (8.44)	52.74 (8.33)

Notes: MPSS = Mood and Physical Symptoms Scale; SD = standard deviation.

4.3.2 Strength of Desire to smoke

The mean (SD) values for SoD at T1 were 3.85 (1.84), 3.85 (1.53), and 4.70 (1.72) for walking, ISO exercise and control condition respectively. The mean (SD) values for SoD at T2 were 4.25 (1.59), 4.05 (1.57), and 4.90 (1.55) for walking, ISO exercise and control condition respectively, and the mean (SD) values for SoD at T3 were 4.60 (1.57), 4.30 (1.84), and 4.90 (1.48) for walking, ISO exercise and control condition respectively (**Figure 5**). The linear mixed regression model identified a significant overall effect of treatment ($p < 0.001$) and an overall effect of time ($p < 0.001$) on SoD; no treatment/time significant interaction was found ($p = 0.155$; **Table 4**).

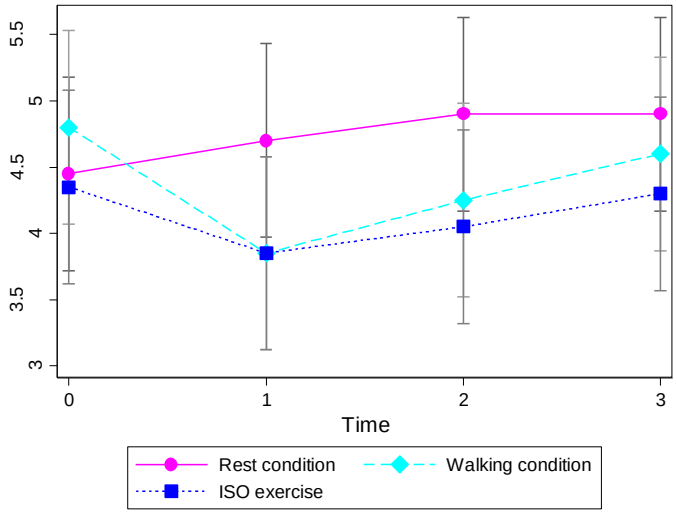


Figure 5 The effects of walking and ISO exercise on Strength of Desire
Notes: Results adjusted with 95% Confidence Intervals; T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

Table 4 Strength of Desire; results of a linear mixed model

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	0.35 (-0.25; 0.95)	1.14 (0.25)
	ISO	-0.1 (-0.67; 0.45)	-0.33 (0.74)
Time	T1	0.25 (-0.35; 0.85)	0.82 (0.41)
	T2	0.45 (-0.15; 1.05)	1.47 (0.14)
	T3	0.45 (-0.15; 1.05)	1.47 (0.14)
Treatment/ time interaction	Walk/T1 interaction	-1.20 (-2.05; -0.35)	-2.77 (0.01)
	Walk/T2 interaction	-1.00 (-1.85; -0.15)	-2.31 (0.02)
	Walk/T3 interaction	-0.65 (-1.50; 0.20)	-1.50 (0.11)
	ISO/T1 interaction	-0.75 (-1.60; 0.10)	-1.73 (0.08)
	ISO/T2 interaction	-0.75 (-1.60; 0.10)	-1.73 (0.08)
	ISO/T3 interaction	-0.50 (-1.35; 0.35)	-1.16 (0.29)
Wald chi^2 statistic		Chi^2 = 33.13, df = 11, p < 0.001	
Global Wald chi^2 statistic treatment		Chi^2 = 15.59, df = 2, p < 0.001	
Global Wald chi^2 statistic of the time		Chi^2 = 8.18, df = 3, p = 0.042	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 9.35, df = 6, p = 0.155	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” (T0) was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2; ISO = isometric exercise condition; Walk = walking condition.

As a sensitivity analysis, a linear mixed model using only one post treatment measurement of cravings (T1) was applied (Appendix D **Table 46**). The linear mixed regression model identified an overall effect of time (p = 0.034) and a non-significant overall effect of treatment (p = 0.121). Interestingly, a significant treatment/time interaction was identified (p = 0.032). The post hoc contrast tests revealed that there was a significant difference between walking and the rest control condition post intervention (T1: z = -2.60, p = 0.009), and between ISO exercise and rest condition post intervention (T1: z = -2.60, p = 0.009; **Figure 5**).

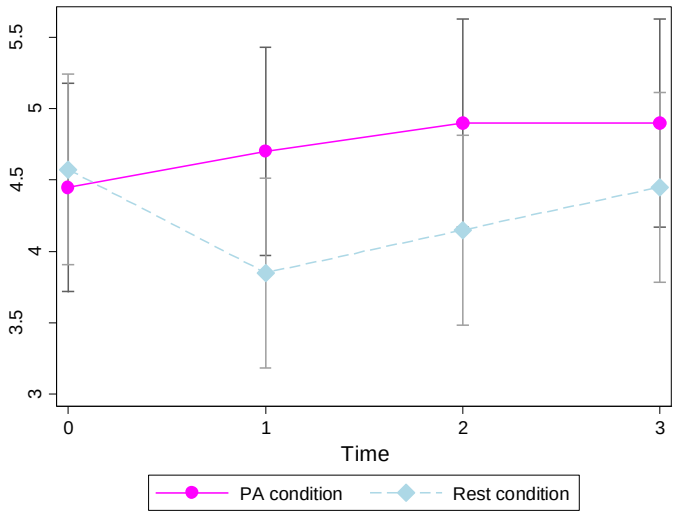


Figure 6 The effects of physical activity condition on Strength of Desire; walking and ISO exercise combined
Notes: Results adjusted with 95% Confidence Intervals; ISO = isometric exercise condition; T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

Finally, a sensitivity analysis where both walking and ISO exercise condition were combined into the "PA condition" and compared with the control rest condition was performed (Appendix D **Table 47**). The linear mixed regression model identified a significant overall effect of treatment (p < 0.001) and non-significant overall effect of time (p = 0.197). Again, a significant

treatment/time interaction was identified (p = 0.042). The post hoc contrast tests revealed that there was a significant difference between PA condition and the rest control condition post intervention (T1: z = -3.21, p = 0.001) and after the post second probe task measurement (T2: z = -2.83, p = 0.005; **Figure 6**).

4.3.3 Desire to smoke

The mean (SD) values for DtS at T1 were 3.80 (1.79), 3.90 (1.83), and 4.55 (1.93) for walking, ISO exercise and control condition respectively. The mean (SD) values for DtS at T2 were 4.25 (1.80), 4.15 (1.98), and 4.85 (1.84) for walking, ISO exercise and control condition respectively. The mean (SD) values for DtS at T3 were 4.55 (1.99), 4.40 (1.96), and 4.95 (1.53) for walking, ISO exercise and control condition respectively (**Figure 7**).

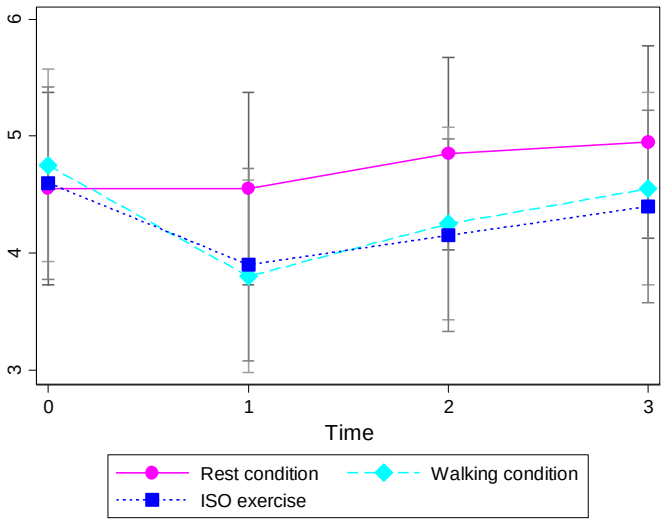


Figure 7 The effects of walking and isometric exercise on Desire to Smoke
Notes: Results adjusted with 95% Confidence Intervals; T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

Similarly to the SoD analysis, the linear mixed regression model identified only a significant overall effect of treatment ($p < 0.001$) and an overall effect of time ($p < 0.001$) on DtS; no treatment/time significant interaction was identified ($p = 0.203$; **Table 5**).

Table 5 Desire to Smoke; results of a linear mixed model

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	0.20 (-0.33; 0.73)	0.74 (0.46)
	ISO	0.05 (-0.48; 0.58)	0.19 (0.85)
Time	T1	0.00 (-0.53; 0.53)	0.00 (1.00)
	T2	0.30 (-0.23; 0.83)	1.11 (0.27)
	T3	0.40 (-0.13; 0.93)	1.49 (0.14)
Treatment/ time interaction	Walk/T1 interaction	-0.95 (-1.70; -0.20)	-2.50 (0.01)
	Walk/T2 interaction	-0.80 (-1.55; -0.05)	-2.10 (0.04)
	Walk/T3 interaction	-0.60 (-1.35; 0.15)	-1.58 (0.12)
	ISO/T1 interaction	-0.70 (-1.45; 0.46)	-1.84 (0.07)
	ISO/T2 interaction	-0.75 (-1.50; -0.00)	-1.97 (0.05)
	ISO/T3 interaction	-0.60 (-1.35; 0.14)	-1.58 (0.12)
Wald chi^2 statistic		$Chi^2 = 38.88$, df = 11, $p < 0.001$	
Global Wald chi^2 statistic treatment		$Chi^2 = 13.60$, df = 2, $p < 0.001$	
Global Wald chi^2 statistic of the time		$Chi^2 = 16.78$, df = 3, $p < 0.001$	
Global Wald chi^2 statistic of the treatment/time interaction		$Chi^2 = 8.52$, df = 6, $p = 0.203$	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" (T0) was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2; ISO = isometric exercise condition; Walk = walking condition.

As a sensitivity analysis, a linear mixed model using only the baseline (T0) and post treatment (T1) cravings measures was applied (Appendix D **Table 48**). The linear mixed regression model identified an overall effect of time ($p = 0.001$). The overall effect of treatment was non-significant ($p = 0.274$), whereas there was weak evidence for significant treatment/time interaction ($p = 0.059$).

The post hoc contrast tests revealed that there was a significant difference between walking and the rest control condition post intervention (T1: z = -2.56, p = 0.010), and between ISO exercise and rest condition post intervention (T1: z = -2.22, p = 0.026; **Figure 7**).

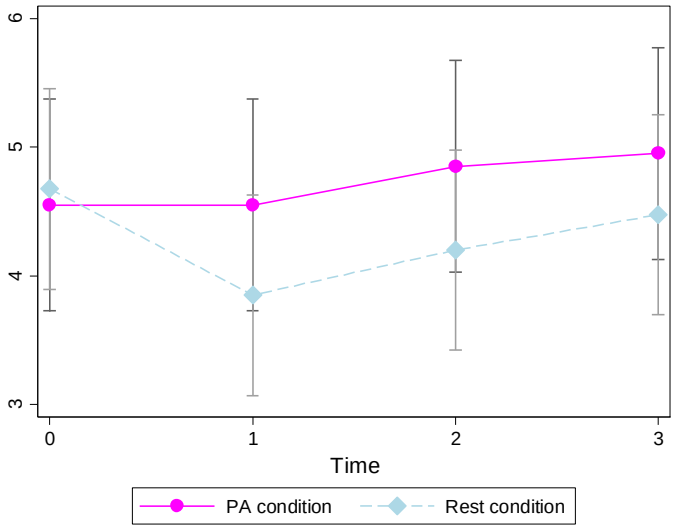


Figure 8 The effects of physical activity condition on Desire to Smoke; walking and ISO exercise combined
Notes: Results adjusted with 95% Confidence Intervals; ISO = isometric exercise condition; T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

In addition, a sensitivity analysis where both walking and ISO exercise condition were combined into the "PA condition" and compared with the control rest condition was performed (Appendix D **Table 49**). The linear mixed regression model identified an overall effect of time (p = 0.012), an overall effect of treatment (p < 0.001), and a significant treatment/time interaction was identified (p = 0.045). The post hoc contrast tests revealed that there was a significant difference between PA condition and the rest control condition post intervention (T1: z = -3.02, p = 0.002), post second probe task measurement

(T2: z = -2.81, p = 0.005), and five minutes post T2 (T3: z = -2.05, p = 0.040; **Figure 8**).

4.3.4 Mood and Physical Symptoms Scale

The mean (SD) values for MPSS at T1 were 1.61 (0.60), 1.38 (0.43), and 1.98 (0.74) for walking, ISO exercise and control condition respectively. The mean (SD) values for MPSS at T2 were 1.71 (0.56), 1.72 (0.49), and 2.12 (0.76) for walking, ISO exercise and control condition respectively, and the mean (SD) values for MPSS at T3 were 1.73 (0.64), 1.64 (0.55), and 2.08 (0.80) for walking, ISO exercise and control condition respectively (**Figure 9**).

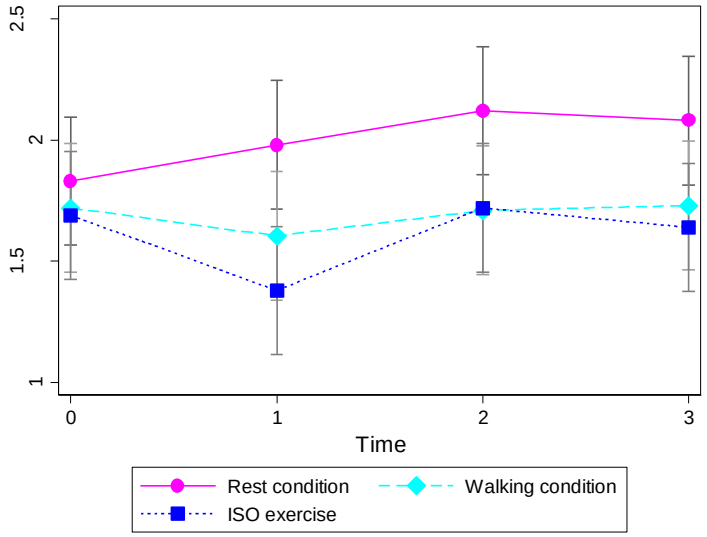


Figure 9 The effects of walking and ISO exercise on Mood and Physical Symptoms Scale
Notes: Results adjusted with 95% Confidence Intervals; T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

The linear mixed regression model identified an overall effect of treatment ($p < 0.001$) and an overall effect of time ($p = 0.033$); however, no treatment/time significant interaction was identified ($p = 0.202$; **Table 6**).

Table 6 Mood and physical symptoms scale; results of a linear mixed model

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	-0.11 (-0.35; 0.13)	-0.89 (0.38)
	ISO	-0.14 (-0.38; 0.10)	-1.13 (0.26)
Time	T1	0.15 (-0.09; 0.39)	1.21 (0.23)
	T2	0.29 (0.05; 0.53)	2.34 (0.02)
	T3	0.25 (0.01; 0.49)	2.09 (0.04)
Treatment/ time interaction	Walk/T1 interaction	-0.27 (-0.61; 0.08)	-1.51 (0.13)
	Walk/T2 interaction	-0.30 (-0.64; 0.04)	-1.71 (0.09)
	Walk/T3 interaction	-0.24 (-0.58; 0.10)	-1.37 (0.17)
	ISO/T1 interaction	-0.46 (-0.80; -0.12)	-2.62 (0.01)
	ISO/T2 interaction	-0.26 (-0.60; 0.08)	-1.48 (0.08)
	ISO/T3 interaction	-0.30 (-0.64; 0.04)	-1.71 (0.09)
Wald chi^2 statistic		$Chi^2 = 62.36$, df = 11, $p < 0.001$	
Global Wald chi^2 statistic treatment		$Chi^2 = 45.12$, df = 2, $p < 0.001$	
Global Wald chi^2 statistic of the time		$Chi^2 = 8.71$, df = 3, $p = 0.033$	
Global Wald chi^2 statistic of the treatment/time interaction		$Chi^2 = 8.53$, df = 6, $p = 0.202$	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” (T0) was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2; ISO = isometric exercise condition; Walk = walking condition.

As a sensitivity analysis, a linear mixed model using only the baseline (T0) and post treatment (T1) cravings measures was applied (Appendix D **Table 50**). The linear mixed regression model identified an overall effect of treatment ($p < 0.001$) and non-significant overall effect of time ($p = 0.225$). Interestingly, a significant treatment/time interaction was identified ($p = 0.044$). The post hoc contrast tests revealed that there was a significant difference between walking and the rest control condition post intervention (T1: $z = -2.87$, $p = 0.004$), and between ISO exercise and rest condition post intervention (T1: $z = -4.59$, $p < 0.001$; **Figure 9**).

Finally, a sensitivity analysis where both walking and ISO exercise condition were combined into PA condition and compared with the control rest condition was performed (Appendix D **Table 51**). The linear mixed regression model identified an overall effect of treatment ($p < 0.001$) and overall effect of time ($p = 0.046$). However, a significant treatment/time interaction was not identified ($p = 0.091$; **Figure 10**).

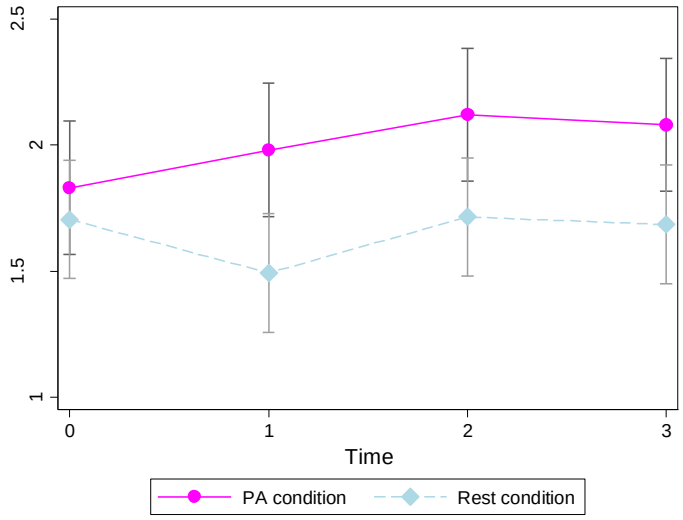


Figure 10 The effects of physical activity condition on Mood And Physical Symptoms Scale; walking and ISO exercise combined
Notes: Results adjusted with 95% Confidence Intervals; ISO = isometric exercise condition; T0 = baseline; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

4.3.5 Maintenance attentional bias

Overall, participants completed 86.7% of critical trials (555/640; 640 = number of critical trials multiplied by number of participants: 32*20) and 87.7% of critical trials (561/640) in the control rest condition at the baseline and post-treatment measurement respectively. Similarly, participants completed 88.1% (564/640) and 85.5% (547/640) of critical trials in the walking condition at the

baseline and post-treatment measurement respectively. Finally, participants completed 87.0% (564/640) and 84.2% (547/640) of critical trials in the ISO exercise condition at the baseline and post-treatment measurement respectively.

The mean values of percentage of dwell time at baseline and post-treatment are presented in **Table 7**.

Table 7 Attentional bias; maintenance attentional bias

Percentage of dwell time	Pre		Post	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Rest condition	54.2 (8.2)	51.6 (47.7; 59.1)	55.1 (9.1)	53.3 (48.5; 60.7)
Walking condition	53.9 (8.2)	51.8 (48.9; 59.5)	51.2 (9.1)	48.2 (46.5; 59.4)
ISO Exercise condition	53.8 (8.8)	51.8 (46.9; 60.8)	55.6 (8.7)	53.1 (51.0; 59.1)

Notes: Maintenance attentional bias are expressed as percentage of dwell time on smoking images; IQR = interquartile range; ISO exercise = isometric exercise; Post = post intervention; Pre = baseline; SD = standard deviation.

The linear mixed regression model was not significant ($p = 0.103$). No overall effect of treatment ($p = 0.093$), no overall effect of time ($p = 0.986$), and no treatment/time interaction effect ($p = 0.111$) was identified (**Table 8** and **Figure 11**).

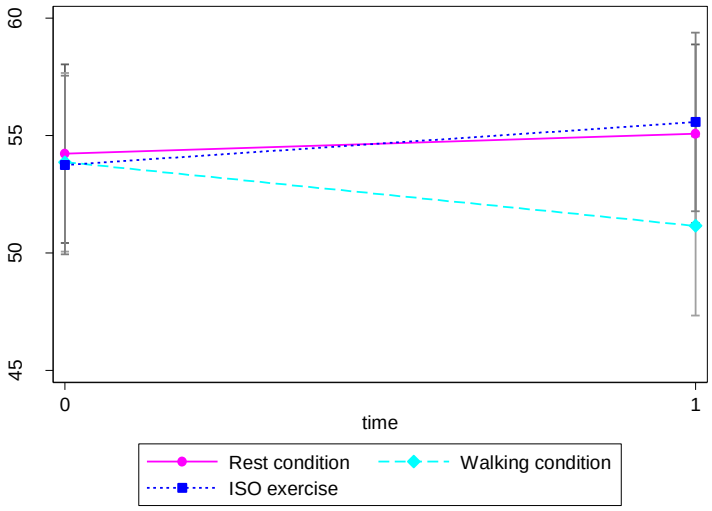


Figure 11 Attentional bias; percentage of dwell time
Notes: Results adjusted with 95% Confidence Intervals; T0 = baseline; T1= post intervention.

Table 8 Dwell time; results of a linear mixed model using only baseline and post treatment cravings values

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	-0.37 (-3.52; 2.79)	-0.23 (0.820)
	ISO	-0.49 (-3.64; 2.67)	-0.30 (0.763)
Time	T1	0.84 (-2.32; 4.00)	0.52 (0.601)
Treatment/ time interaction	Walk/T1 interaction	-3.56 (-8.02; 0.91)	-1.56 (0.118)
	ISO/T1 interaction	0.98 (-3.48; 5.45)	0.43 (0.666)
Wald chi^2 statistic		Chi^2 = 9.16 df = 5, p = 0.103	
Global Wald chi^2 statistic treatment		Chi^2 = 4.75, df = 2, p = 0.093	
Global Wald chi^2 statistic of the time		Chi^2 = 0.00, df = 1, p = 0.985	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 4.40, df = 2, p = 0.111	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" (T0) was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; ISO = isometric exercise condition; Walk = walking condition.

In addition, a sensitivity analysis where both walking and ISO exercise conditions were combined into the "PA condition" and compared with the control rest condition was performed (Appendix D **Table 52**). Similarly, the linear mixed

regression model was not significant (p = 0.678). No overall effect of treatment (p = 0.291), no overall effect of time (p = 0.845), and no treatment/time interaction effects (p = 0.526) were identified.

4.3.6 Initial attentional bias

Similarly, the mean values of percentage of first fixation at baseline and post-treatment are summarised in **Table 9.**

Table 9 Attentional bias; initial attentional bias

Percentage of initial fixations	Pre Mean (SD)	Median (IQR)	Post Mean (SD)	Median (IQR)
Rest condition	55.6 (11.9)	55.6 (49.2; 59.7)	51.1 (8.5)	51.7 (45.1; 56.3)
Walking condition	50.9 (8.5)	51.6 (46.6; 56.0)	48.8 (6.1)	48.1 (43.2; 53.6)
ISO Exercise condition	52.5 (8.5)	51.0 (46.6; 60.0)	50.7 (7.6)	53.6 (43.3; 56.1)

Notes: Initial attentional bias are expressed as percentage of dwell time on smoking images; IQR = interquartile range; ISO exercise = isometric exercise; Post = post intervention; Pre = baseline; SD = standard deviation.

The linear mixed regression model was not significant (p = 0.209). No overall significant effect of treatment (p = 0.186), or time (p = 0.075) were identified, also the treatment/time interaction effect was non-significant (p = 0.735; **Table 10** and **Figure 12**). In addition, a sensitivity analysis where both walking and ISO exercise conditions were combined into the “PA condition” and compared with the control rest condition was performed (Appendix D **Table 53).** Again, the linear mixed regression model was not significant (p = 0.096). No significant overall effect of treatment, (p = 0.111) was identified, whereas there

was weak evidence for an overall effect of time (p = 0.051); no treatment/time interaction effect (p = 0.434) was identified.

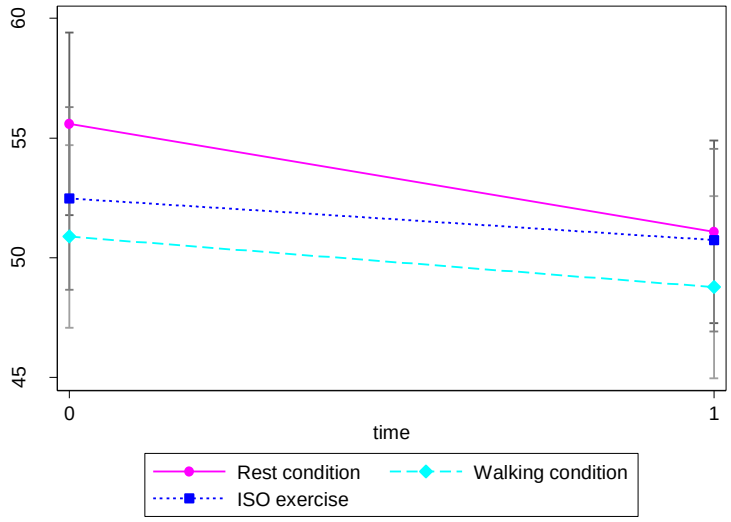


Figure 12.Attentional bias; percentage of initial fixations
Notes: Results adjusted with 95% Confidence Intervals; T0 = baseline; T1= post intervention.

Table 10 First fixation; results of a linear mixed model

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	-4.71 (-10.02; 0.60)	-1.74 (0.082)
	ISO	-3.12 (-8.43; 2.19)	-1.15 (0.250)
Time	T1	-4.51 (-9.81; 0.80)	-1.66 (0.096)
Treatment/ time interaction	Walk/T1 interaction	2.39 (-5.11; 9.90)	0.63 (0.532)
	ISO/T1 interaction	2.77 (-4.74; 10.27)	0.72 (0.470)
Wald chi^2 statistic		Chi^2 = 7.16, df = 5, p = 0.209	
Global Wald chi^2 statistic treatment		Chi^2 = 3.37, df = 2, p = 0.185	
Global Wald chi^2 statistic of the time		Chi^2 = 3.17, df = 1, p = 0.075	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 0.61, df = 2, p = 0.735	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" (T0) was the baseline category for time; 95 % CI = 95% Confidence Interval; T1= post intervention; ISO=isometric exercise condition; Walk = walking condition

4.3.7 Reaction time attentional bias score

Due to technical difficulties reaction data for one participant were not recorded; data from 19 participants were analysed. Overall, participants made errors in 3.1% (19/608; 608 = number of critical trials multiplied by number of participants with valid data: 32*19) and 5.26% (32/608) of critical trials in the control rest condition at baseline and post-treatment measurements respectively. Similarly, participants made errors in 3.0% (18/608) and 3.8% (23/608) of critical trials in the walking condition at baseline and post-treatment measurements respectively. Finally, participants made errors in 3.6% (22/608) and 4.4% (27/608) of critical trials in the ISO exercise condition at baseline and post-treatment measurements respectively.

Table 11 Attentional bias; reaction time attentional bias score

Reaction time attentional bias score	Pre Mean (SD)	Median (IQR)	Post Mean (SD)	Median (IQR)
Rest condition	16.50 (45.67)	9.12 (-8.61; 26.33)	42.46 (68.53)	27.36 (-7.79; 54.57)
ISO Exercise condition	14.99 (52.77)	2.05 (-33.15; 58.71)	28.61 (51.08)	13.06 (-3.94; 59.44)
Walking condition	17.26 (48.28)	-0.23 (-12.93; 44.13)	19.46 (34.63)	17.09 (6.72; 50.04)

Notes: IQR = interquartile range; ISO exercise = isometric exercise; Post = post intervention; Pre = baseline; SD = standard deviation

The mean values of percentage of first fixation at baseline and post-treatment are summarised in **Table 11**; positive values of reaction time AB score suggest AB towards smoking images.

The linear mixed regression model was not significant (p = 0.258). No overall effect of treatment (p = 0.470) was found, whereas there was weak evidence for a significant effect of time (p = 0.066), also no treatment/time interaction effect (p = 0.440; **Table 12** and **Figure 13**) was identified.

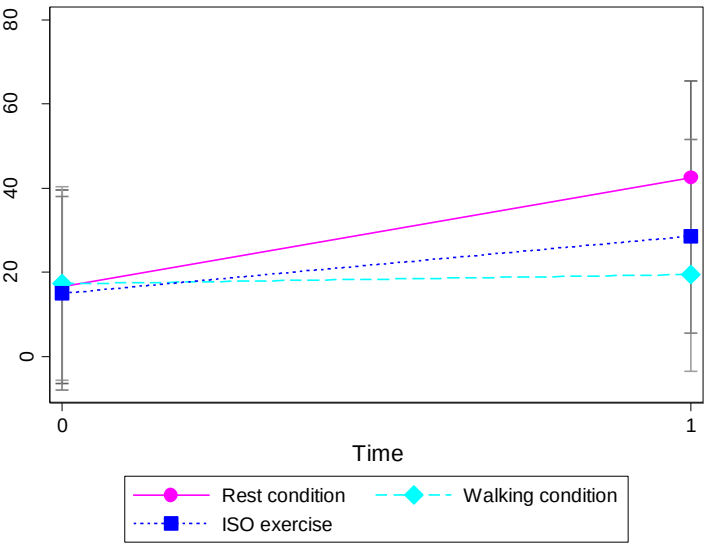


Figure 13 Attentional Bias; Reaction Time Attentional Bias Score
Notes: Results adjusted with 95% Confidence Intervals; T0 = baseline; T1 = post intervention.

In addition, a sensitivity analysis with both walking and ISO exercise conditions combined into one "PA condition" and compared with the control rest condition was performed (Appendix D **Table 54**). Again, the linear mixed regression model was not significant (p = 0.106). No overall effect of treatment, (p = 0.238), a significant overall effect of time (p = 0.034), and no treatment/time interaction effect (p = 0.258) was identified.

Table 12 Reaction Time Attentional Bias Score; results of a linear mixed model using only baseline and post treatment cravings values

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	0.76 (-24.96; 26.47)	0.06 (0.954)
	ISO	-1.52 (-27.24; 24.19)	-0.12 (0.907)
Time	T1	25.96 (0.25; 51.67)	1.98 (0.048)
Treatment/time interaction	Walk/T1 interaction	-23.76 (-60.12; 12.60)	-1.28 (0.200)
	ISO/T1 interaction	-12.33 (-48.70; 24.03)	-0.66 (0.506)
Wald chi^2 statistic		Chi^2 = 6.53 df = 5, p = 0.258	
Global Wald chi^2 statistic treatment		Chi^2 = 1.51, df = 2, p = 0.470	
Global Wald chi^2 statistic of the time		Chi^2 = 3.38, df = 1, p = 0.066	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 1.64, df = 2, p = 0.440	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" (o) was the baseline category for time; 95 % C I= 95% Confidence Interval; T1 = post intervention; ISO = isometric exercise condition; Walk = walking condition.

4.3.8 Associations between cigarette cravings and attentional bias

The associations between cigarette cravings and AB post intervention (T1) were assessed using Spearman correlations (**Table 13**); a significant association was found between DtS and maintenance AB at T1 for control condition (rho = 0.60, p=0.034).

Table 13 Cigarette cravings and attentional bias; correlations

		SoD		DtS	
		rho	p-value	rho	p-value
Maintenance AB	**Control**	0.26	0.267	0.60	0.034
	Walk	0.12	0.605	0.16	0.271
	ISO	0.23	0.339	0.67	0.170
Initial AB	**Control**	0.05	0.849	-0.22	0.357
	Walk	-0.19	0.435	0.01	0.952
	ISO	-0.05	0.847	-0.15	0.521
Reaction time AB score	**Control**	0.22	0.723	0.11	0.663
	Walk	0.13	0.917	0.02	0.945
	ISO	0.58	0.626	0.03	0.893

Notes: AB = attentional bias; ISO = isometric exercise condition; Walk = walking condition; rho = Spearman correlation coefficient.

4.4 Discussion

These results support previous acute studies' conclusions (e.g.Faulkner et al. 2010; Janse Van Rensburg and Taylor 2008; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Ussher et al. 2009; Ussher et al. 2006) and suggest that 10 minutes of walking and 10 minutes of ISO exercise are both beneficial in decreasing cigarette craving and withdrawal. However, the effect of the two PA interventions on SoD, DtS and MPSS was identified only in the sensitivity analyses.

When the sensitivity analyses included only the first post treatment measurement (T1), significant differences between the walking condition and the control condition, and between the ISO exercise condition and the control condition, were identified for SoD, DtS and MPSS. The results of the sensitivity analyses may suggest that the effects of the two PA interventions on cigarette cravings and MPSS do not last long after the intervention. The qualitative Cochrane review suggested that the effects of PA on cravings and withdrawal last up to 30 minutes post exercise (Ussher et al. 2012). When the two PA conditions were combined sensitivity analyses, significant differences between the combined PA condition and the control condition were identified for cravings; SoD (T1 – T2) and DtS (T1 – T3).

Alternatively, the inclusion of the probe task and the use of the eye-tracking device (including the calibration process before and after the eye-tracking measurements were taken) in the study design delayed the

measurements of cravings (T2 and T3), and the effects of the two PA interventions could have been weakened. As such, the design of the current study may have been too complex to detect the effects of two different types of PA on the outcomes of interest even if they existed, and is a potential limitation of the current study. In addition, similarly to one other study (Cooke et al. 2014), compared with the systematic review, the cravings' SD reported in the current study appeared to be larger when compared with the studies included in the review (Haasova et al. 2013). Finally, the current study reported the third lowest cravings out of the 19 included studies included in the review (Haasova et al. 2013).

Conversely, the strengths of the study were the recruitment of moderately heavy smokers with moderate levels of cravings (after temporary abstinence), and a different, perhaps more rigorous method of statistical analysis. In comparison, studies included in the recent systematic review used a variation of more traditional methods such as analyses of covariance and t-tests (Haasova et al. 2013).

No effects of PA on AB were found. The only other study that investigated the effects of PA on AB, found significant effects of 15 minutes of PA on maintenance and initial AB in 20 temporarily abstaining smokers; they reported size eta^2 of 0.416 and eta^2 of 0.343 for maintenance and initial AB respectively (Janse Van Rensburg et al. 2009a). In addition, no association between cigarette cravings and AB (apart from maintenance AB at T1 in control

condition: rho = 0.60, p=0.034) was found. It is believed that a weak association between AB (especially for indirect measures of AB) and cigarette cravings exists (Field et al. 2009b). However, the complicated design of the current study, the dot probe reliability and methodological issues (Ataya et al. 2012; Field and Christiansen 2012; Field et al. 2009a; Schmukle 2005), and the fact that wearing an eye-tracker may have disrupted performance on the dot probe task, limits the generalizability of the AB results.

In agreement with other AB research, the results of this study support the use of the eye-tracking methodology in a more real world settings (Ataya et al. 2012; Field and Christiansen 2012; Field et al. 2009a; Janse Van Rensburg et al. 2009a; Schmukle 2005). One study used the eye-tracking technology outside a laboratory setting; they found that smokers, compared with non-smokers, made significantly more fixations to smoking cues in an office space environment while completing a sham experimental task (Baschnagel 2013). Similarly, a laboratory based study used the eye-tracking technology with pictures of real world scenes (e.g. a dinner scene) and found that smokers, compared to non-smokers, made significantly more fixations and spent more time attending to smoking cues (Bonitz and Gordon 2008).

Further research is needed to determine the effects of PA on AB, and to establish the relationship between AB and cravings and other smoking outcomes. Based on the results of the current study, using a simple parallel arms design with two conditions (e.g. control and PA conditions), pre and post

treatment measurement of AB with 80% power to detect approximately 10% change in the maintenance and initial AB, 104 and 70 participants would be needed respectively (Appendix D **Table 55**). The study results including the above power calculations, highlighted the difficulty of small studies to exhaustively answer research questions (Button et al. 2013).

4.5 Conclusion

This study suggests that 10-minute bouts of walking and ISO exercise have beneficial effects on cigarette cravings and withdrawal symptoms in temporarily abstaining smokers. It appeared that both modes of PA, walking and ISO exercise, had similar effects on cigarette cravings and withdrawal symptoms. Smokers wishing to use PA as a smoking cessation aid may choose to use either walking or seated ISO exercise, depending on situational constraints and personal preferences. However, the number of acute studies investigating the effects of PA (Taylor et al. 2007) and results of this study suggest that a systematic review and a meta-analysis (if data allow) of studies investigating the effects of PA on cigarette cravings and withdrawal symptoms may better address these issues. In addition, to answer the question of what attributes of PA are associated with changes in cigarette cravings and withdrawal symptoms, an IPD meta-analysis where data are available on the type of exercise performed by each participant may be appropriate. Finally, future studies investigating the effects of PA on AB, may wish to apply eye-tracking methodology in a more real world setting.

Chapter 5: The acute effects of physical activity on cigarette cravings: Systematic review and individual participant data meta-analysis

5.1 Introduction

Previous systematic reviews concluded that there is good evidence that physical activity (PA) reduces cigarette cravings acutely (Taylor et al. 2007; Ussher et al. 2012); however, this phenomenon has not been quantified using the most rigorous statistical approach. Also, the growth of research (Ussher et al. 2012) suggests a need to update the evidence on the acute effects of PA on cigarette cravings. A recent study summarised the acute effects of PA on cigarette cravings, withdrawal symptoms, affect, and smoking behaviour, but they did not use individual participant data (IPD) and included only 10 studies in the meta-analyses (Roberts et al. 2012). Although an IPD meta-analysis is more time-consuming than aggregate meta-analysis (Stewart and Tierney 2002), it enables exploratory analyses such as heterogeneity examination, increases the power to detect any treatment effects across individuals in randomised trials, and offers many advantages over aggregate meta-analysis (Chalmers 1993; Lyman and Kuderer 2005).

This study aimed to update the current evidence on the acute effects of PA on cigarette cravings, following a systematic review (Taylor et al. 2007), and

to collate IPD for use in quantifying the effects of PA on cigarette cravings. In summary, the research question explored in this chapter is:

- What are the effects of short bouts of PA on cigarettes cravings in temporarily abstaining smokers and can any such effects be quantified?

5.2 Methods

5.2.1 Search strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conduction and reporting systematic reviews were followed (Moher et al. 2009). A systematic review of literature was conducted, following the methodology described by Taylor and colleagues (Taylor et al. 2007). 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. The search was restricted to publications written in English and to articles published from 2004 onwards (the previous review conducted searches until July 2006). All searches were conducted between 1st April and 31st May 2011. The search strategy for the electronic databases was: “(smoking or smoking cessation) and (exercise or physical activity) and (craving$ or withdrawal)”.

5.2.2 Inclusion/exclusion criteria

To be eligible for inclusion, studies must have examined effects of acute PA on either Desire to Smoke (DtS; Tiffany and Drobes 1991) or Strength of Desire to Smoke (SoD; West and Hajek 2004; West et al. 1989; West and Russell 1985). 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 (West et al. 1999) from the Mood and Physical Symptoms Scale (West and Hajek 2004; West and Russell 1985) 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 2 hours prior to baseline measurement, which increases baseline cigarette cravings (Katomeri unpublished). Acute studies involving participants who were taking part in a cessation programme or were using nicotine replacement therapy (NRT) were excluded, as baseline cravings may be low, and this review sought to determine the effects of PA on strong cravings, as experienced typically in the first hours and days of cessation. To avoid publication bias, both published and unpublished studies were included.

5.2.3 Data extraction and synthesis

Information regarding individual participants' pre- and post-treatment cravings levels (DtS and/or SoD measures), and the treatment condition(s) 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 the values were adjusted (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 (Oh and Taylor 2014; Thompson unpublished).

5.2.4 Inclusion of cross-over trials

Cross-over trials have an inherent risk of carry-over effects. The treatment given in the first period could have an effect that carries over to the second period. In addition, the effects of order (of the treatments) and interactions between treatment and period need to be investigated before including cross-over trials in a meta-analysis (Elbourne et al. 2002). All eligible studies conducted testing on different days with smokers having the opportunity to smoke ad libitum between the tests. In addition, the longest lasting reported

effects of acute PA on cigarette cravings is of 30 minutes' duration (Ussher et al. 2009). Thus the risk of carry-over and intervention order effects in all cross-over design studies were considered extremely low. Therefore mixed linear regression models with a random intercept on participant (to allow adjustment for multiple observations on individual participants) were used to analyse to cross-over studies (Brown and Prescott 1999).

5.2.5 Statistical 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, more prominence was given to the RE methods (Borenstein et al. 2009; Riley et al. 2011). Although technically ordinal variables rather than continuous, these variables were treated as continuous outcome (as in the primary studies) for the purpose of the analyses, and to facilitate the use of linear modelling.

Both two-stage models and one-stage models were used. It was anticipated that results would be similar. The one-stage model allows investigation of factors at a patient-level (Lambert et al. 2002) and the two-stage model allows visual presentation of results in the form of forest plots, and

facilitates quantification of heterogeneity. 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; Brown and Prescott 1999) 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) and I^2 methods (Higgins and Thompson 2002; Higgins et al. 2003).

For the one-stage meta-analyses, studies were combined using a mixed linear regression model (Higgins et al. 2001), with random intercepts on study and participant (to adjust for clustering due to multiple participants within each study, and due to 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 (Lyratzopoulos et al. 2012). 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* -1.96*b*; *a* + 1.96*b*. For 95% of studies, the true mean difference between intervention groups lies within this range. All analyses were performed using Stata v. 11.

5.3 Results

5.3.1 Literature search

The database searches yielded 544 items. After including studies from others resources, such as a previous review by Taylor and colleagues (Taylor et al. 2007), SRNT meeting abstracts, responses to key list-serves, reference searches, and communication with published authors and excluding duplicates, 411 titles were identified. Next, 353 articles were excluded based on the title. Two reviewers further examined 58 abstracts. Thirty six studies investigating the effects of various types of PA on cigarette cravings in smokers were identified (Arbour-Nicitopoulos et al. unpublished; Bock et al. 1999; Daley et al. 2004; Daniel unpublished; Daniel et al. 2004; Daniel et al. 2006; 2007; Elibero et al. 2011; Everson et al. 2006; 2008; Faulkner et al. 2010; Haasova et al. unpublished; Harper et al. 2012; 2013; Ho et al. 2014; Janse Van Rensburg unpublished; Janse Van Rensburg et al. 2013; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Katomeri unpublished, study 4; Mikhail unpublished; Oh and Taylor 2014; Pomerleau et al. 1987; Reeser unpublished; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Thayer et al. 1993; Thompson unpublished; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006; Williams et al. 2010). See the flow diagram for more details (**Figure 14**).

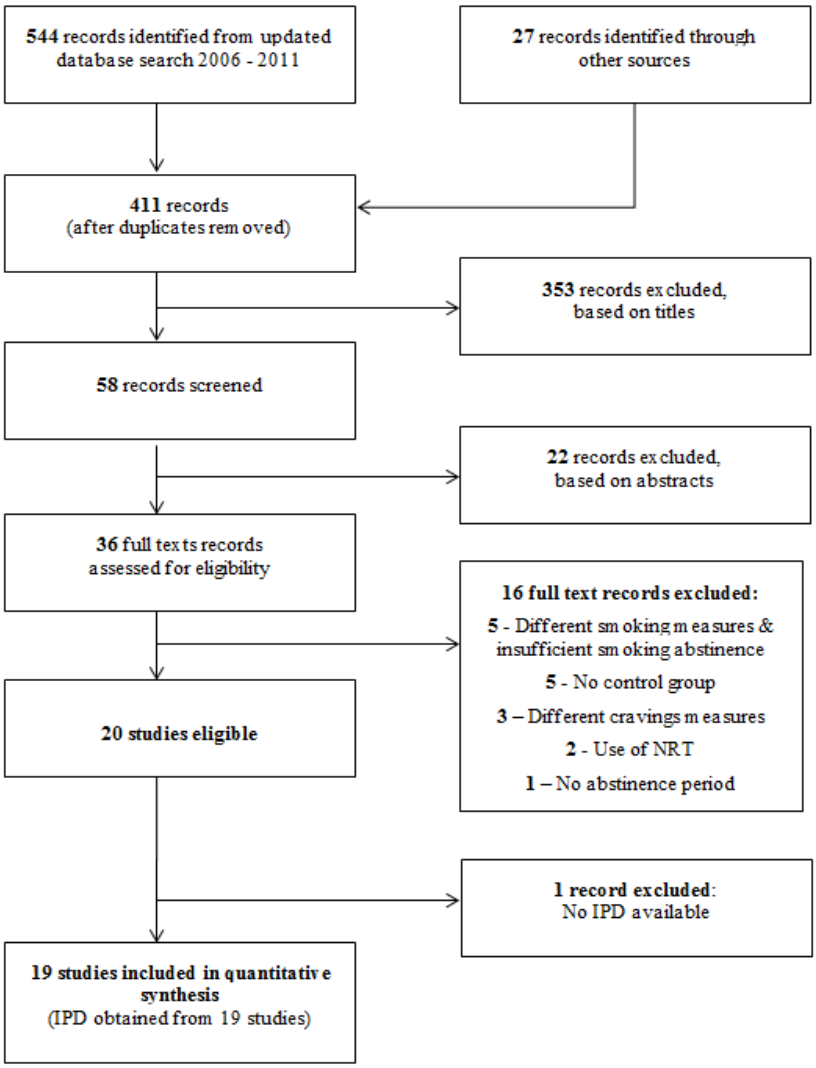


Figure 14. Flow diagram of study retrieval process

However, only 20 studies were found to be eligible and primary authors were contacted to provide raw IPD (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Faulkner et al. 2010; Haasova et al. unpublished; Ho et al. 2014; Janse Van Rensburg unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Oh and Taylor 2014; Scerbo et al. 2010; Taylor and Katomeri 2007;Katomeri, unpublished #4605; Taylor et al. 2005;

Thompson unpublished; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006). IPD could not be obtained from one study (Ho et al. 2014), and thus this study was excluded from the analyses. Appendix E **Table 56** and Appendix E **Table 57** describes included and excluded studies respectively.

5.3.2 Study characteristics and quality assessment

Among the 19 RCTs included in the meta-analysis, 7 studies used a parallel arm design (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Taylor and Katomeri 2007; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006) and 12 studies used a cross-over design (Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor et al. 2005; Thompson unpublished;Janse Van Rensburg, unpublished #6840). There were 14 published studies (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Faulkner et al. 2010; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006), three PhD projects (Haasova et al. unpublished; Katomeri unpublished; Oh and Taylor 2014), one MSc project (Thompson unpublished) and one unpublished study by Janse Van Rensburg. The duration of the PA/control interventions ranged from 5–40 minutes. The number of participants in each study varied from 10–84. One study (Ussher et al. 2009) 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) only the laboratory based results were included. Both cravings measures were taken immediately before the intervention and immediately after (Daniel et al. 2004; Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor and Katomeri 2007;Janse Van Rensburg, unpublished #6840; Taylor et al. 2005; Thompson unpublished; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006) or 5 minutes after the intervention (Daniel et al. 2006; Everson et al. 2008; Janse Van Rensburg and Taylor 2008).

Studies investigated the effects of moderate intensity walking (Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg and Taylor 2008; Katomeri unpublished; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Thompson unpublished), running (Scerbo et al. 2010; Thompson unpublished), moderate intensity cycling (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg et al. 2012;Janse Van Rensburg, unpublished #6840; Oh and Taylor 2014; Ussher et al. 2001), vigorous intensity cycling (Everson et al. 2008; Oh and Taylor 2014), isometric exercise (Haasova et al. unpublished; Ussher et al. 2009; Ussher et al. 2006) and light intensity cycling (Daniel et al. 2004). Intensity of PA in studies was described using rate of perceived exhaustion (RPE; Borg 1998), percentage of heart rate (HR) max, HR reserve or a combination of these methods. All control conditions were passive.

Fifteen studies used sitting passively (Daniel et al. 2004; Everson et al. 2008; Faulkner et al. 2010; Janse Van Rensburg unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Thompson unpublished; Ussher et al. 2001; Ussher et al. 2006), some control conditions included sitting passively and listening to an audio recording (Haasova et al. unpublished; Ussher et al. 2009), a cognitive task (Daniel et al. 2006), watching a video (Ussher et al. 2001), and body scanning techniques (Ussher et al. 2009; Ussher et al. 2006). Both studies investigating body scanning techniques suggested a positive effect of body scanning on cravings reduction (Ussher et al. 2009; Ussher et al. 2006), although body scanning was coded as a control condition in the meta-analyses because it does not involve any bodily movement.

Overall, 13 studies used both DtS and SoD as a measure of cigarette cravings (Daniel et al. 2004; Daniel et al. 2006; Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Thompson unpublished; Ussher et al. 2001; Ussher et al. 2006), two studies used SoD only (Everson et al. 2008; Ussher et al. 2009) and four studies used DtS only (Janse Van Rensburg unpublished ; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008).

Table 14. Strength of Desire and Desire to Smoke in included studies

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 and colleagues (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 and colleagues (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 and colleagues (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 and colleagues (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 (unpublished)	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 and colleagues (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 and colleagues (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 and colleagues (2008)	4.97 (1.67)	3.23 (1.85)	4.27 (1.44)	4.27 (1.67)	NA	NA	NA	NA
Janse Van Rensburg and colleagues (2008)	NA	NA	NA	NA	4.87 (1.18)	4.09 (1.44)	5.00 (1.17)	5.30 (0.97)
Janse Van Rensburg and colleagues (2009a)	NA	NA	NA	NA	5.15 (1.76)	3.15 (2.21)	5.40 (1.35)	5.05 (1.50)
Janse Van Rensburg and colleagues (2009b)	NA	NA	NA	NA	4.80 (1.48)	3.10 (1.45)	4.40 (1.84)	4.80 (1.69)
Thompson (unpublished)	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 and colleagues (2009)	5.50 (1.45)	3.71 (1.33)	5.18 (1.59)	3.82 (1.40)	NA	NA	NA	NA
Faulkner and colleagues (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 and colleagues (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 and Taylor (2014)	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 and colleagues (unpublished)	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 and colleagues (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 (unpublished)	NA	NA	NA	NA	4.62 (1.61)	3.69 (2.18)	5.00 (1.21)	5.58 (0.90)

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); SD = standard deviation; PA = physical activity; Pre = baseline; Post = post intervention.

Table 14 describes baseline cravings for SoD and DtS for all 19 studies. Three studies reported only one outcome measure in their published data

(Faulkner et al. 2010; Taylor et al. 2005; Ussher et al. 2006), but all three studies had collected both SoD and DtS measures of cigarette cravings. However IPD for both cravings was collected (Faulkner et al. 2010; Taylor et al. 2005; Ussher et al. 2006), therefore both SoD and DtS measures were included the analyses. In addition, cravings 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 were included (Faulkner et al. 2010).

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 recruitment order (Scerbo et al. 2010).

Strength of Desire

SoD was the main outcome in 15 studies providing 797 observations; 440 in PA and 457 in control condition. Seven of these studies were parallel arm studies (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Taylor and Katomeri 2007; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006) and eight were cross-over studies (Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor et al. 2005; Thompson unpublished). Five of the parallel arm studies (Daniel et al. 2004; Everson et al. 2008; Ussher et al. 2009;

Ussher et al. 2001; Ussher et al. 2006), included three arms in their design. Passive and body scanning conditions were both considered to be control arms (Ussher et al. 2009; Ussher et al. 2006). Similarly, both video watching and the sitting condition were considered to be a control arm in one study (Ussher et al. 2001). Both moderate cycling and vigorous cycling were considered to be PA treatment arms (Everson et al. 2008). Both light and moderate cycling were coded as PA conditions for one study (Daniel et al. 2004). Four of the cross-over design studies (Haasova et al. unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Thompson unpublished) included three arms in their design. Treadmill running and walking (Scerbo et al. 2010), vigorous and moderate cycling (Oh and Taylor 2014), treadmill running and walking (Thompson unpublished), and treadmill walking and isometric exercise (Haasova et al. unpublished) were combined; all of these conditions were considered to be 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 (Daniel et al. 2004; Daniel et al. 2006; Taylor and Katomeri 2007; Ussher et al. 2001; Ussher et al. 2006) and 12 were cross-over studies (Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor et al. 2005; Thompson unpublished). Three of the parallel arms studies (Daniel et al. 2004; Ussher et al. 2001; Ussher et al.

2006) included three arms in their design. Again, passive and body scanning conditions (Ussher et al. 2006), video watching and passive condition (Ussher et al. 2001) were considered to be control conditions, whereas both light cycling and passive condition (Daniel et al. 2004) were considered to be a PA condition. Four of the cross-over design studies (Haasova et al. unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Thompson unpublished) included three arms in their design. Treadmill running and walking (Scerbo et al. 2010), vigorous and moderate cycling (Oh and Taylor 2014), treadmill running and walking (Thompson unpublished), and treadmill walking and isometric exercise (Haasova et al. unpublished) were combined; all of these conditions were considered to be PA.

Table 15. Desire to Smoke; Individual Participant Data Meta-Analyses

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

Notes: CI = Confidence Interval; ES = Effect Size: for the two-stage MA, the ES is a Cohen's d and for the one-stage MA the ES is the between group mean difference; 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

5.3.3 Individual participant data meta-analysis

The individual random effects meta-analysis results are summarised in **Table 15** and **Table 16** and are appraised in the discussion section.

Table 16. Strength of desire to smoke; individual participant data meta-analyses

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

Notes: CI = Confidence Interval; ES = Effect Size: for the two-stage MA, the ES is a Cohen's d and for the one-stage MA the ES is the between group mean difference; MA = meta-analysis; N = number of observations; I^2 = heterogeneity measure; p values from Q-statistic; negative ES favours intervention and positive ES favours control condition.

5.3.4 All eligible studies (both parallel arms 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. **Figure 15** shows the associated forest plots for SoD.

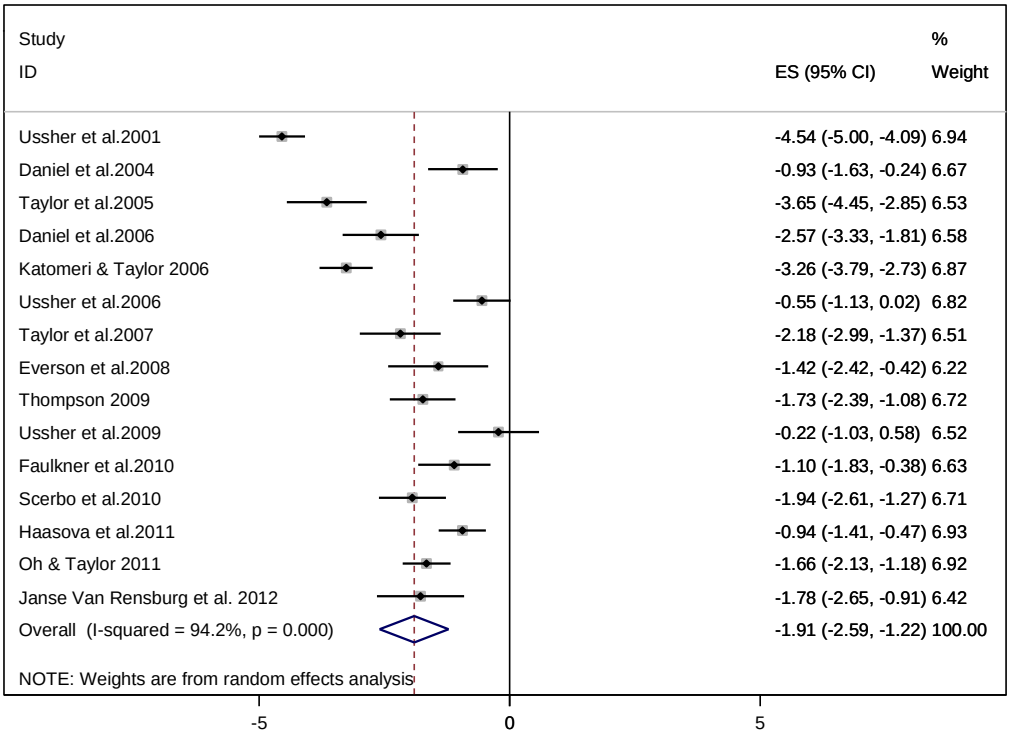


Figure 15. Strength of Desire to smoke; forest plot using all eligible studies

Notes: Results from individual participant data meta-analysis of all studies using 2-stage random effects regression of post SoD with baseline adjustment. Negative ES favours intervention and positive ES favours control condition. ES = effect size in terms of the mean difference between the PA and control groups for post-intervention SoD within each trial; SoD = Strength of Desire to smoke; 95% CI = 95% confidence intervals.

A 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). **Figure 16** shows the associated forest plots for DtS.

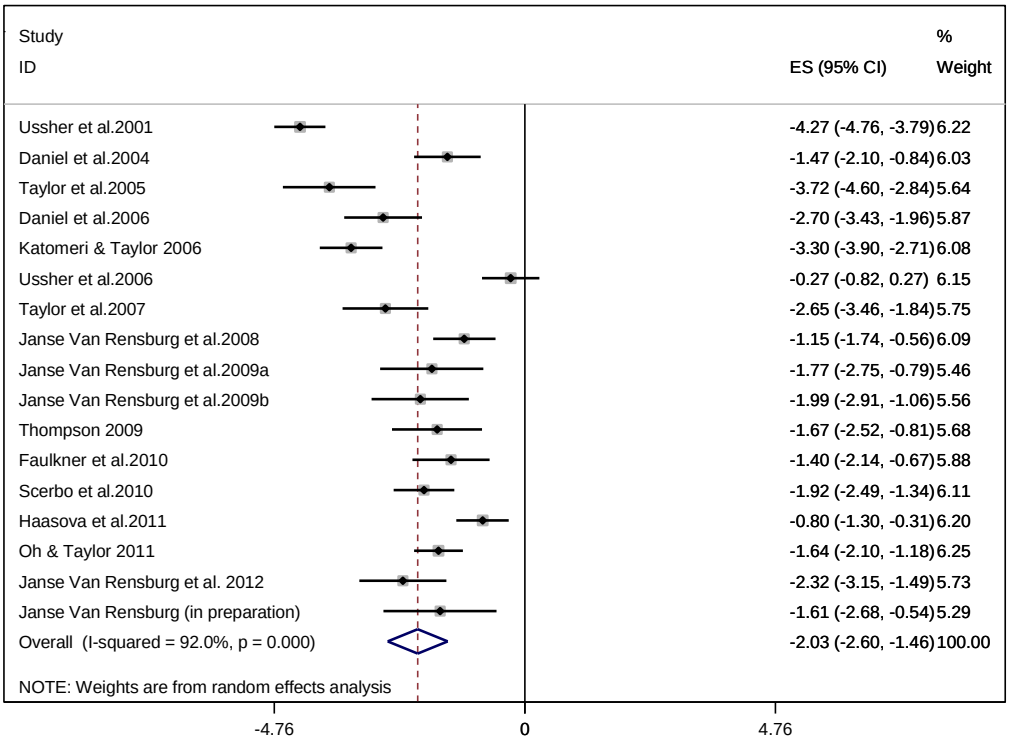


Figure 16. Desire to Smoke; forest plot using all eligible studies
Notes: Results from individual participant data meta-analysis of all studies using 2- stage random effects regression of post DtS with study and baseline. Negative ES favours intervention and positive ES favours control condition. ES = effect size in terms of the mean difference between the PA and control groups for post-intervention DtS within each trial; DtS = Desire to Smoke; 95% CI = 95% confidence intervals.

When analysing published and unpublished studies separately results in the same direction with moderately higher values for DtS than SoD in both published and unpublished studies were observed. A two-stage IPD RE meta-analysis of 11 published studies with SoD (Daniel et al. 2004; Daniel et al. 2006; Faulkner et al. 2010; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Ussher et al. 2001; Ussher et al. 2006) 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 (Daniel et al. 2004;

Daniel et al. 2006; Everson et al. 2006; 2008; Faulkner et al. 2010; Janse Van Rensburg et al. 2012; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006) 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 (Haasova et al. unpublished; Oh and Taylor 2014; Thompson unpublished) 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 (Haasova et al. unpublished; Janse Van Rensburg unpublished; Katomeri unpublished; Oh and Taylor 2014; Thompson unpublished) 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.

5.3.5 Parallel arm studies

Two-stage random effects meta-analysis

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). **Figure 17** and **Figure 18** show the associated forest plots for SoD and DtS, respectively.

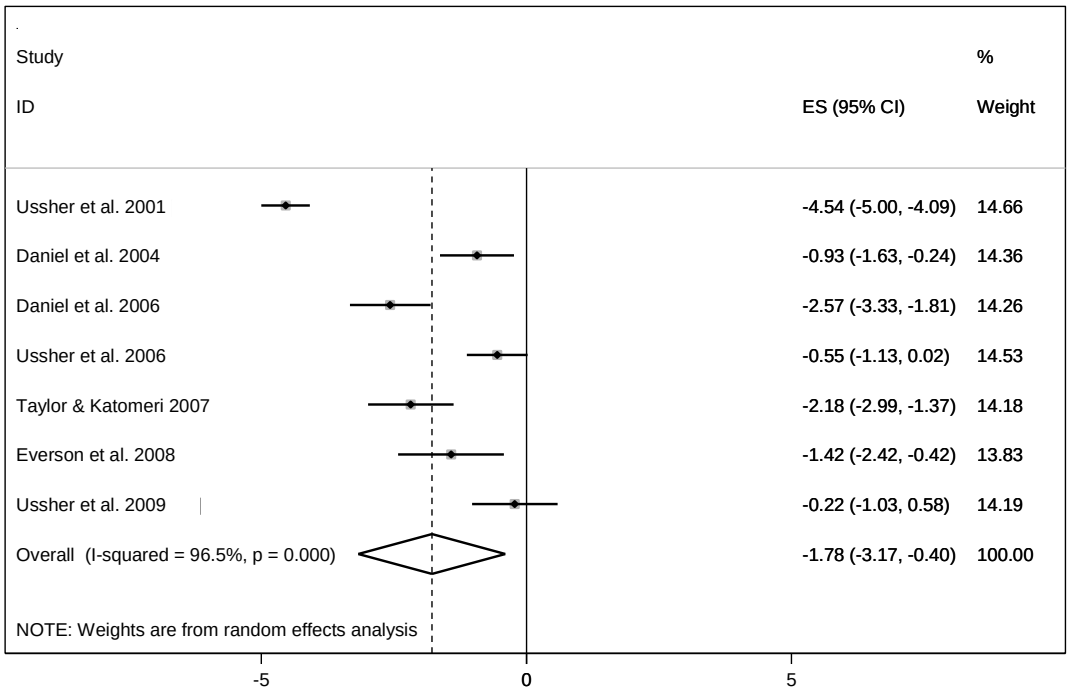


Figure 17. Strength of Desire to smoke; forest plot using only parallel arm design studies

Notes: Results from 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 Negative ES favours intervention and positive ES favours control condition. ES = effect size in terms of the mean difference between the PA and control groups for post-intervention SoD within each trial; SoD = Strength of Desire to smoke; 95% CI = 95% confidence intervals.

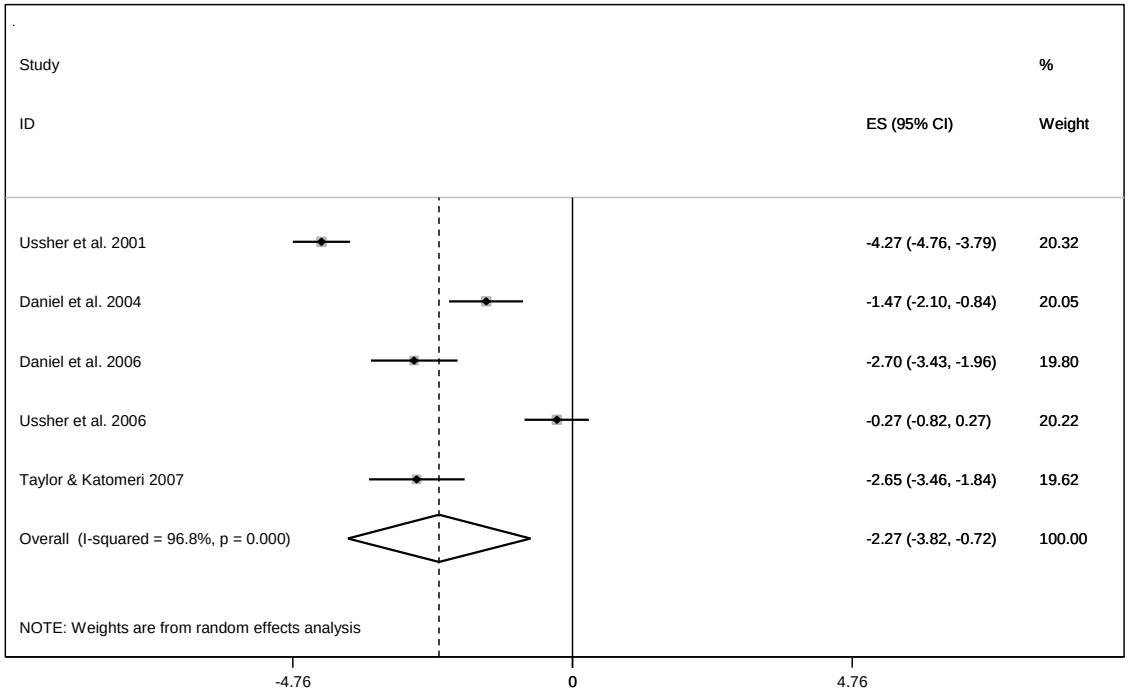


Figure 18. Desire to Smoke; forest plot using only parallel arm design studies

Notes: Results from 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. Negative ES favours intervention and positive ES favours control condition. ES = effect size in terms of the mean difference between the PA and control groups for post-intervention DtS within each trial; DtS = Desire to Smoke; 95% CI = 95% confidence intervals.

5.3.6 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, it was 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 (Daniel et al. 2004; Daniel et al. 2006; Faulkner et al.

2010; Haasova et al. unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor et al. 2005; Taylor et al. 2007; Thompson unpublished; Ussher et al. 2001) and 13 studies with SoD as the main outcome (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Haasova et al. unpublished; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor et al. 2005; Taylor et al. 2007; Thompson unpublished; Ussher et al. 2001). All studies compared either moderate cycling (ten studies) or moderate walking (seven 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). **Figure 19** and **Figure 20** show the associated forest plots for SoD and DtS, respectively.

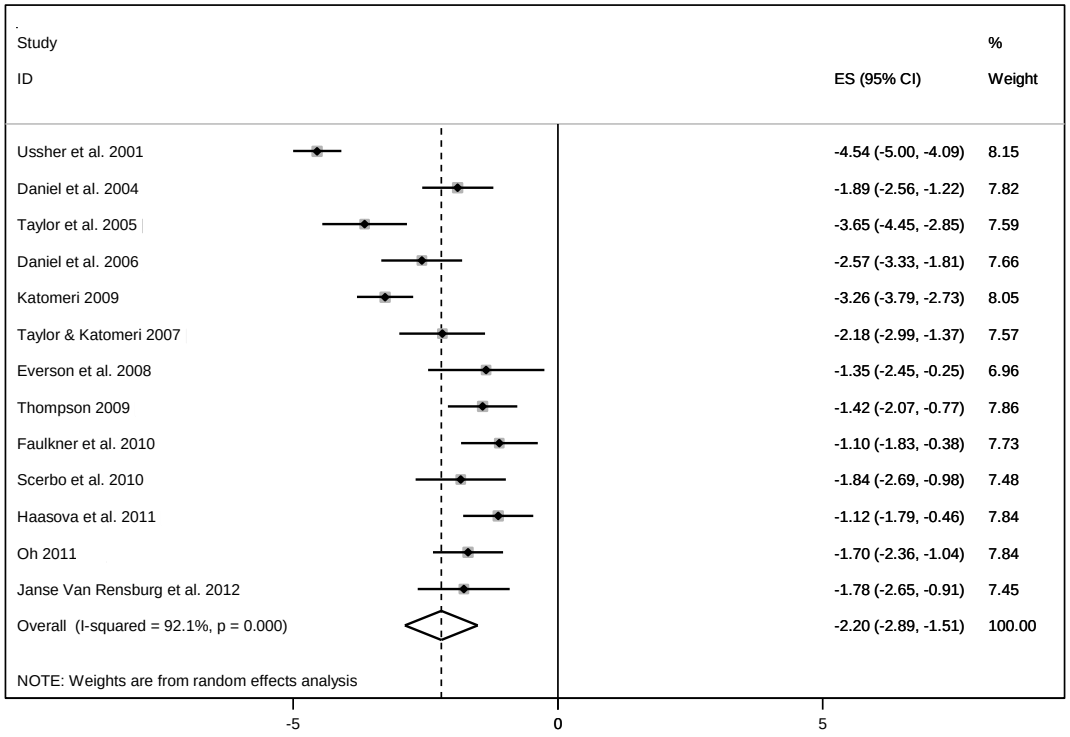


Figure 19. Strength of Desire to smoke; forest plot using only studies comparing control condition with moderate physical activity

Notes: Results from 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. Negative ES favours intervention and positive ES favours control condition. ES = effect size in terms of the mean difference between the PA and control groups for post-intervention SoD within each trial; SoD = Strength of Desire to smoke; 95% CI = 95% confidence intervals.

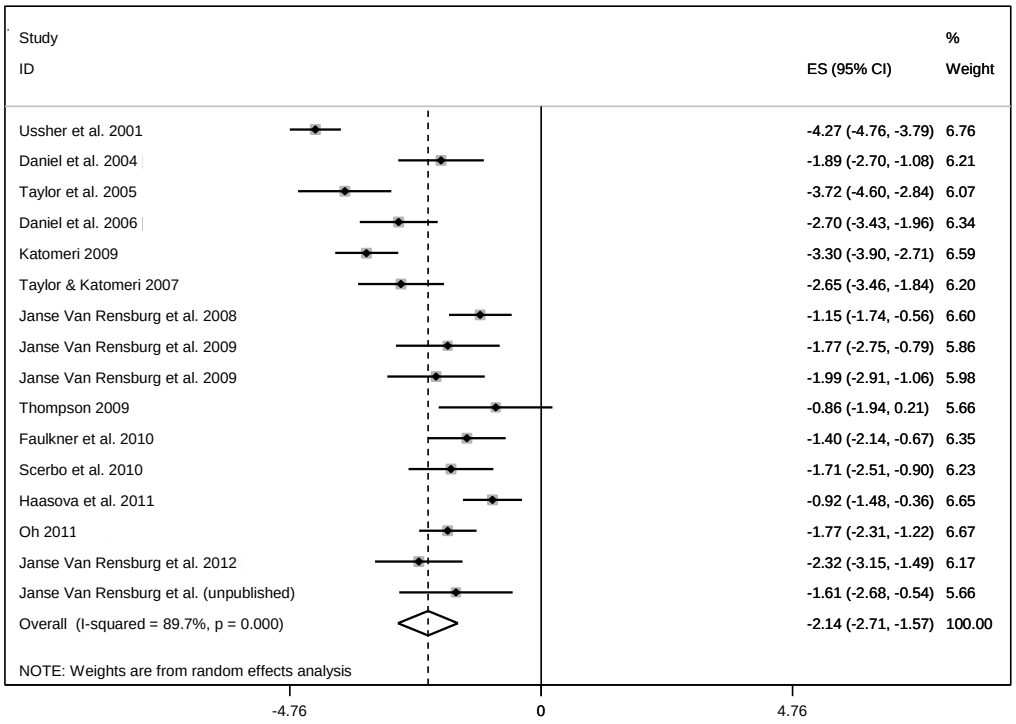


Figure 20. Desire to Smoke; forest plot using only studies comparing control condition with moderate physical activity

Notes: Results from 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 Negative ES favours intervention and positive ES favours control condition. ES = effect size in terms of the mean difference between the PA and control groups for post-intervention DtS within each trial; DtS = Desire to Smoke; 95% CI = 95% confidence intervals.

5.4 Discussion

All analyses suggest that short bouts of PA acutely decrease cigarette cravings (**Table 15** and **Table 16**) and confirm conclusions from previous narrative reviews (Taylor et al. 2007; Ussher et al. 2012). IPD from one study were not obtained (Ho et al. 2014); 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, very similar results compared to analyses including all studies were found; cross-over design studies produced 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 IPD were obtained for both outcome measures, while only one outcome was reported in the associated publication. When the comparison was narrowed down to only moderate-intensity PA versus controls, the effect sizes were somewhat larger. This suggests that the observed effects of PA on cigarette cravings may vary by intensity of PA (and possibly type and duration of PA also), and therefore the potential associations between aspects of PA on cigarette cravings need to be further investigated.

These results were similar to those reported in a recent review (Roberts et al. 2012), 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 (Arbour-Nicitopoulos et al.). Similarity of the results may suggest that the effects of acute PA on cigarette cravings are robust. The study (Ussher et al. 2001) 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 14**).

This study (Ussher et al. 2001) also used slightly older participants (mean age = 36 years) than other studies. Two other studies that produced larger effect sizes (effect size > -3;) (Katomeri unpublished; Taylor et al. 2005) also had high initial cravings (**Table 14**). However, other studies also had high baseline cravings (i.e., > 5) and did not produce such large effect sizes. In contrast, all studies investigating isometric exercise (Haasova et al. unpublished; Ussher et al. 2009; Ussher et al. 2006) had the smallest effect sizes, with a 95% CI including 0 in two cases for SoD (Ussher et al. 2009; Ussher et al. 2006) and in one case for DtS (Ussher et al. 2006). The results from the above mentioned studies further support the idea that type 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, both passive and body scanning conditions were considered to be control conditions. However, both studies investigating body scanning suggested a positive effect of body scanning (compared with passive control) on cigarette cravings (Ussher et al. 2009; Ussher et al. 2006). On removing the body scanning conditions from the analysis (comparing sitting control condition with PA), the effect sizes of both studies increased (but remained low). When the isometric exercise condition was removed from a study comparing a walking condition and an isometric exercise condition with a control condition (Haasova et al. unpublished), the effect size increased. Similarly, when light cycling was excluded from the analysis (Daniel et al. 2004), 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 PA, which was statistically significant across all meta-analyses. The magnitude of the cravings reduction after short bouts of PA is comparable and exceeding the cravings reduction associated with NRT and glucose (Cahill et al. 2012; Taylor et al.

2007), and this may have practical implications for the use of PA as a smoking cessation aid.

5.5 Conclusion

This is the first study to quantify the acute effects of PA on cigarette cravings using IPD meta-analysis. 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-level demographic and smoking characteristics as potential moderators of the effect of PA on cigarette cravings is necessary. Potential differences in the effects of variable aspects of PA, such as type, duration and intensity, on cigarette cravings should also be investigated.

Chapter 6: The acute effects of physical activity on cigarette cravings: Exploration of moderators, mediators and physical activity attributes using systematic review and individual participant data meta-analyses

6.1 Introduction

Systematic reviews have demonstrated positive effects of acute bouts of physical activity (PA) in reducing cigarette cravings in abstaining smokers (Haasova et al. 2013; Roberts et al. 2012; Taylor et al. 2007; Ussher et al. 2012). These effects have been quantified in a recent meta-analysis using individual patient data (IPD), which showed a significant reduction in cravings of approximately 30% for participants engaging in a form of PA, compared with participants in passive condition (Haasova et al. 2013). Cigarette cravings were recorded on a scale of 1–7 using self-reported measures of cravings; Desire to Smoke (DtS; Tiffany and Drobes 1991) and Strength of Desire to Smoke (SoD; West and Hajek 2004; West and Russell 1985). IPD meta-analyses enable exploration of potential patient-level predictors of the outcome variable, such as demographic covariates, as well as the potential for moderation and mediation of the effects of the intervention being investigated (Lyman and Kuderer 2005; Riley et al. 2010).

The circumplex model of affect (Russell 1980), proposes that all affective states arise from two dimensions; one related to valence (a pleasure–

displeasure continuum), assessed by the Feeling Scale (FS; Hardy and Rejeski 1989) and the other related to arousal, assessed by the Felt Arousal Scale (FAS; Svebak and Murgatroyd 1985). Temporary smoking abstinence leads to a decrease in arousal and an increase in emotional stress, which both return to a normal level after smoking a cigarette (Steptoe and Ussher 2006). The Nesbitt's Paradox, when smoking increases sympathetic arousal, yet smokers report feelings of relaxation and contentment, was explained using evidence that smoking a cigarette has independent effects on arousal and emotional stress (Parrott 1998). A meta-analysis of 158 studies found that a single session of aerobic exercise resulted in moderate increases in affective activation (Cohen's d = 0.47, standard deviation = 0.37) from pre- to post-treatment (Reed and Ones 2006). Also, another review noted increases in affective valence in response to a single session of exercise with considerable inter-individual variability occurring at high PA intensities (Ekkekakis et al. 2011). It has been suggested that changes in affect, as a result of PA, may mediate effects of PA on cigarette cravings (Taylor et al. 2007). Indeed, eight studies designed to investigate the acute effects of exercise on cravings found changes in affect following PA, but have been underpowered to assess the mediating effects on cravings of changes in affect due to PA. In addition, the availability of IPD allows exploration of the correlation between the two measures of cigarette cravings (DtS and SoD) used across the primary studies. In summary, the research questions explored in this chapter are:

- Are there any potential predictors or moderators of the effect of PA on cigarette cravings?

- Is it possible to identify any mediating mechanisms by which PA influences cigarette cravings (e.g. affective activation or valence)?
- Are there any specific features of PA (such as type, intensity or duration) that have differential effects on cigarette cravings?

This information may help practitioners prescribe PA more effectively to smokers attempting to quit. This chapter aims to address these issues using IPD meta-analysis methods.

6.2 Methods

The earlier meta-analysis (Haasova et al. 2013) followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conducting and reporting systematic reviews. Nineteen studies (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Faulkner et al. 2010; Haasova et al. unpublished; Janse Van Rensburg unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Janse Van Rensburg et al. 2012; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005; Thompson unpublished; Ussher et al. 2009; Ussher et al. 2001; Ussher et al. 2006) reported acute cigarette cravings among temporarily abstaining smokers and contributed IPD to the current analyses. The search strategy, inclusion and exclusion criteria, data extraction, and data handling were described in Chapter 5. The MacArthur guidelines (Kraemer et al. 2002) were followed in analyses of moderators and mediators. All statistical analyses were performed using Stata v. 11.

6.2.1 Cravings measures

The two cravings measures were used, Desire to Smoke (DtS; Tiffany and Drobes 1991) and Strength of Desire to Smoke (SoD; West and Hajek 2004; West et al. 1989; West and Russell 1985). Both DtS and SoD are assessed using a seven-point Likert scale. 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 (West et al. 1999) from

the Mood and Physical Symptoms Scale (West and Hajek 2004; West and Russell 1985) and is assessed with the statement 'How strong is your desire to smoke right now?' (1 = not at all, 4 = somewhat, 7 = extremely). To facilitate the use of linear regression modelling and to assist with interpretation of the results, all responses on the 1–7 scale were linearly rescaled to a range of 0–100 (Lyratzopoulos et al. 2012). Thus, a mean difference between groups of -10 would indicate that post-intervention cravings were 10 percentage lower in the intervention group compared with the control group. Spearman correlation coefficients were used to investigate the association between the two measures of cravings within individuals who had observations available for both DtS and SoD at the same time point (baseline or post-intervention). If the correlation between the two cravings measures was found to be high, it may be justifiable to combine studies using these different outcome variables in the same meta-analysis.

6.2.2 Potential predictors, moderators and mediators

Selection of potential predictors of cigarette cravings, and moderators of the effects of PA on cravings, was of necessity dependent on the availability of participant-level data in the primary studies. The previous IPD meta-analysis suggested that age and nicotine dependence may moderate the acute effects of PA on cigarette cravings (Haasova et al. 2013); hence, these characteristics were investigated as potential predictors and moderators in the analyses. Exploratory analyses encompassed additional potential predictors and moderators, such as gender, and body mass index (BMI), weekly PA levels and

resting heart rate, since there is some evidence that inactive and/or overweight smokers may experience reduced pleasure following exercise (Ekkekakis et al. 2011). Smoking characteristics such as the Fagerström Test of Cigarette Dependence (FTCD; Fagerström 1978; 2012), abstinence period, carbon monoxide measures taken prior to the start of the intervention, and number of years the participant had been smoking, were also included as potential predictors and/or moderators in the analyses. Participants were categorised as being physically active (≥ 150 minutes of moderate or vigorous activity in a week) or inactive (< 150 minutes of moderate or vigorous activity in a week), to explore the effects of participants' baseline PA levels on the effects of acute bouts of PA on cigarette cravings. The Seven-day Physical Activity Recall Questionnaire (Blair et al. 1985) was used in five studies, The International Physical Activity Questionnaire (Craig et al. 2003) was used in three studies and one study used a cut-off of 30 minutes on 5 or fewer days per week. Changes in affect were suggested to mediate the acute effects of PA on cigarette cravings (Taylor et al. 2007), hence we included measures of affect (FAS and FS) as potential mediators in our analyses. Similarly to the cravings outcomes, to facilitate interpretation of results and to calculate change scores for affect, both FS (measured on a Likert scale of -5 to +5) and FAS (measured on a Likert scale of 1–6) scores, were linearly rescaled to 0–100 (Lyratzopoulos et al. 2012).

6.2.3 Physical activity attributes

Chapter 5 suggested that some aspects of PA, such as intensity of exercise, may influence the effects of acute PA on cigarette cravings. We therefore categorised all treatment conditions in terms of intensity, duration and type. In the primary studies, intensity of PA in studies was described using Rating of Perceived Exertion (RPE; Borg 1998), percentage of maximum heart rate, heart rate reserve or combinations of these methods.

Three PA intensity categories were defined: light, moderate and vigorous. Moderate intensity exercise was investigated in 17 studies, 8 of these investigating the effects of walking and 9 investigating the effects of cycling. Vigorous intensity exercise was investigated in four studies, two investigating the effects of cycling and two of running. Six studies investigated the effects of light intensity exercise, one investigating the effects cycling, two of walking, and three of isometric exercise.

There were three PA duration categories: short (PA of 5 minutes' duration), medium (PA of 10 minutes' duration) and long (PA of 15 minutes' duration or longer). Two studies used a PA intervention of 5 minutes' duration, seven studies used a PA intervention of 10 minutes' duration, and one study used a self-paced one-mile walk that lasted on average 17 minutes and 48 seconds. Also, there were three types of PA: isometric exercise, cycling and walking/running. All control conditions were passive. **Table 17** summarises all combinations of PA attributes available in the 19 studies for both DtS and SoD.

Table 58 and **Table 59** (Appendix F) summarise the PA attributes available in the 19 studies for DtS and SoD separately.

Table 17. Physical activity attributes combinations investigated in randomised controlled trials

Intensity	Duration	Type	Number of studies	N
Light	Short	Isometric	1	20
		Cycling	1	28
	Medium	Isometric	2	34
Moderate	Short	Cycling	1	28
	Medium	Walking/running	2	43
		Cycling	5	105
	Long	Walking/running	5	127
		Cycling	3	56
Vigorous	Medium	Cycling	1	15
	Long	Walking/running	2	28
		Cycling	1	23

Notes: N = number of observations.

Statistical analyses

Both fixed effect and random effects meta-analysis methods were considered. Due to the heterogeneity of studies with regard to types of PA intervention and participant characteristics, random effects methods were applied to the data (Riley et al. 2010). IPD enables the use of more complex one-stage models (rather than a traditional two-stage approach). One-stage models have advantages over a two-stage model when investigating patient-level sources of heterogeneity, as patient-level characteristics can be

incorporated into the model (Lambert et al. 2002). One-stage IPD meta-analyses (as described in Chapter 5) compared participants engaging in PA against control participants. Mixed linear regression models were used (Higgins et al. 2001), adjusted for baseline values of the outcome variable (DtS/SoD for cravings analyses, and FS/FAS for affect analyses), with a fixed effect on study, random intercept on participant (adjustment for multiple observations within participant for cross-over trials) and random effect on treatment (allowing the treatment effect to vary across studies). An approximate 95% mid-range of the effect size across studies (assuming a normal distribution of treatment effects across studies) was derived using the mean difference between the intervention and control groups and the standard deviation for intervention effect across studies (Lyratzopoulos et al. 2012). If the fixed effect is given by a and the standard deviation (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 the intervention and control groups would lie within this range.

A series of analyses were performed, investigating the effects of the trial interventions (PA and control), with adjustment for individual demographic, psychological and smoking related covariates (described above) on cigarette cravings. In addition, baseline FS and FAS were investigated as potential predictors or moderators of treatment effect. Only variables demonstrating a significant interaction with the intervention were considered to be moderating the effects of acute PA on cigarette cravings (Kraemer et al. 2002). To analyse the potential mediating influence of affect in the relationship between PA and

cigarette cravings, FS and FAS were used as outcomes to determine any effect of PA on affect. Should FS or FAS be found to be associated with PA, the change in FS and FAS (post-treatment score - baseline score) would be used to investigate an association between change in affect and cravings. An interaction between treatment and change in affect would be also added to the model, to determine whether the change in affect had a main effect on outcome (as a mediator of change in cravings) or an interactive effect with treatment (Kraemer et al. 2002).

One-stage IPD meta-analyses investigated all the attributes of PA individually. For example, all PA intensities, light, moderate and vigorous, were individually compared against controls. Random effects were applied to PA attributes (allowing the effects of individual PA attribute categories to vary across studies) only when the between studies variance appeared to be non-zero and was estimated with reasonable precision. An analysis combining all three PA attributes was then performed, identifying the attributes of PA associated with change in cravings, while adjusting for effects of all other PA attributes.

6.3 Results

IPD were available from 19 studies; of these, 17 reported DtS, while 15 reported SoD; only 2 studies reported SoD only. The number of participants in each study varied from 10–84; overall, there were 930 observations in the IPD dataset. All cravings measures were taken immediately before the intervention and immediately after. Studies investigated the effects of moderate intensity walking, running, moderate intensity cycling, vigorous intensity cycling, isometric exercise and light intensity cycling. All control conditions were passive (Appendix E **Table 56**).

6.3.1 Relationship between strength of desire and desire to smoke

The Spearman correlation coefficients (including data from 13 studies where both DtS and SoD were reported) for the relationship between DtS and SoD were high: $r = 0.786$ ($p < 0.01$) at baseline ($n = 703$), and $r = 0.840$ ($p < 0.01$) post intervention ($n = 704$). However, a variation across the individual studies was found. The Spearman correlation coefficients varied from $r = 0.542$ to 0.877 for baseline values, and from $r = 0.685$ to 0.954 for post intervention values (**Table 18**). Of the 19 available studies, 13 studies reported both measures; two studies reported SoD only and four studies reported DtS only. Despite a degree of variability across studies in the correlations between DtS and SoD, the two measures were combined in one cravings outcome. For the main analyses DtS was used as the preferred outcome measure, with SoD used as a proxy for DtS for the two studies that reported SoD only. As a

sensitivity analysis, all analyses were repeated using DtS and SoD as separate outcomes.

Table 18. Spearman correlations of Strength of Desire and Desire to Smoke

Study	n	Design	DtS	SoD	Baseline	Post
Ussher and colleagues (2001)	78	P	✓	✓	0.593	0.853
Daniel and colleagues (2004)	84	P	✓	✓	0.715	0.754
Taylor and colleagues (2005)	30	C	✓	✓	0.862	0.865
Daniel and colleagues (2006)	40	P	✓	✓	0.872	0.954
Katomeri, unpublished	60	C	✓	✓	0.575	0.814
Ussher and colleagues (2006)	60	P	✓	✓	0.782	0.732
Taylor and Katomeri (2007)	60	P	✓	✓	0.635	0.833
Everson and colleagues (2008)	45	P	NA	✓	NA	NA
Janse Van Rensburg and colleagues, 2008	46	C	✓	NA	NA	NA
Janse Van Rensburg and colleagues (2009a)	40	C	✓	NA	NA	NA
Janse Van Rensburg and colleagues (2009a)	20	C	✓	NA	NA	NA
Thompson, unpublished	30	C	✓	✓	0.653	0.718
Ussher and colleagues (2009)	48	P	NA	✓	NA	NA
Faulkner and colleagues (2010)	46	C	✓	✓	0.887	0.924
Scerbo and colleagues (2010)	54	C	✓	✓	0.771	0.935
Haasova and colleagues, unpublished	60	C	✓	✓	0.770	0.685
Oh and Taylor, 2014	69	C	✓	✓	0.798	0.894
Janse Van Rensburg and colleagues (2012)	34[1]	C	✓	✓	0.542	0.745
Janse Van Rensburg and colleagues, unpublished	25	C	✓	NA	NA	NA
All parallel arms studies	332	P	✓	✓	0.793	0.841
All cross over studies	382	C	✓	✓	0.780	0.837
All studies	705[2]	P & C	✓	✓	0.786	0.840

Notes: All correlations were significant at $p < 0.01$; C = cross over design; DtS = desire to smoke; NA = not available, n = number of observations, P = parallel arms design; SoD = strength of desire to smoke; Post = post intervention; 1 = correlation for baseline values included only 33 participants; 2 = correlation for baseline values included only 704 participants.

6.3.2 One-stage individual participant data meta-analyses of physical activity on cigarette cravings

The analyses of the effects of acute PA on cigarette cravings as published in the recent review (Haasova et al. 2013; Chapter 5) were repeated using the 0–100 scale. A one-stage IPD meta-analysis yielded a fixed effect mean difference between groups of -31.56 (-42.14; -20.99) for SoD with an SD on the associated random effect of 14.17; the 95% midrange of intervention effects across studies was -59.33; -3.80. Similarly, a one-stage IPD meta-analysis yielded fixed effect mean difference between groups of -33.77 (95% CI: -42.39 to -25.16) for DtS, with an SD on the associated random effect of 12.04; the 95% midrange of intervention effects across studies was -57.37; -10.18. The new combined cigarette cravings measure was also analysed; a one-stage IPD meta-analysis yielded a fixed effect mean difference between groups of -31.71 (-40.01; -21.41) with an SD on the associated random effect of 12.26; the 95% midrange of intervention effects across studies was -55.74; -7.68. **Table 19** enables a comparison of the results using the original 1–7 Likert scale and the linearly rescaled 0–100 scale for SoD, DtS and the combined cigarette cravings measure.

Table 19 One-stage meta-analyses of the effects of acute physical activity on cigarette cravings and measures of affect.

Outcome	Number of participants (number of studies)	Mean difference (95%CI) 0–100 scales	Mean difference (95%CI) original scales
SoD[1]	797 (15)	-31.56 (42.14, -20.99)	-1.89 (-2.53, -1.26)
DtS[1]	837 (17)	-33.78 (-42.39,-25.16)	-2.03 (-2.54,-1.51)
Combined cravings[1,2]	930 (19)	-31.71 (-40.01,-23.41)	-1.90 (-2.40, -1.40)
FS[3,4]	372 (8)	7.30 (2.64, 11.97)	0.73 (0.26, 1.20)
FAS[3,4]	372 (8)	16.43 (7.53, 25.34)	0.82 (0.38, 1.27)
FS[3,4] (moderate intensity PA only)	318 (8)	8.95 (5.19, 12.70)	0.90 (0.52, 1.27)
FAS[3,4] (moderate intensity PA only)	319 (8)	17.64 (8.64, 26.64)	0.88 (0.43, 1.33)

Notes: All ES were significant at $p < 0.001$; CI = Confidence Intervals; DtS = desire to smoke; FAS = felt arousal scale; FS = feeling scale; SoD: desire to smoke; 1 = negative ES favours intervention. positive ES favours control condition and negative ES favours intervention, 2 = DtS substituted by SoD where no DtS scores were available, 3 = positive ES favours intervention, and negative ES favours control condition, 4 = cravings measure consists of DtS only.

6.3.3 Potential predictors and moderators of cigarette cravings

When included as individual covariates with intervention, only age, BMI and number of years of smoking were significantly associated ($p < 0.05$) with the post-intervention combined cigarette cravings measure. In addition, resting heart rate approached significance ($p = 0.062$). An increase in age and an increase in number of years of smoking were associated with a decrease in cravings post-intervention, whereas an increase in BMI and an increase in resting heart rate were associated with an increase in cravings post-intervention. The associations of all individual covariates with cigarette cravings after intervention are reported in **Table 20**. All models including individual

covariates were extended by including interaction effects with intervention and the covariate. However, no significant interaction effects were found. These results suggest that none of the included covariates acted as a moderator of the effects of PA on cigarette cravings.

The influence of the individually significant predictors was investigated further. In a model including all individually significant predictors and resting heart rate, only BMI ($p = 0.019$) remained significantly associated with the cravings reduction; however, only 178 observations were available. Based on the number of observations available and significance of individual predictors, a final model including BMI and age was considered to be the most appropriate model. Ten studies collected both BMI and age data (Daniel et al. 2004; Daniel et al. 2006; Everson et al. 2008; Faulkner et al. 2010; Haasova et al. unpublished; Katomeri unpublished; Oh and Taylor 2014; Scerbo et al. 2010; Taylor and Katomeri 2007; Ussher et al. 2001). A one-stage IPD random effects meta-analysis (574 observations) yielded a fixed effect mean difference of -0.27 (-0.51; -0.03) for age, and a fixed effect mean difference of 1.10 (0.52; 1.68) for BMI (**Table 20**). Both age and BMI were significantly associated with cravings but did not moderate the effect of PA (the associations between age and BMI, and cravings were the same for both arms). Sensitivity analyses, separate analyses of the two cravings measures (DtS and SoD), showed similar results (Appendix F **Table 60** and **Table 61** respectively).

Table 20. Associations of covariates and the effects of physical activity on cigarette cravings

Covariates		Number of observations	Number of studies	Mean difference (95%CI) 0-100 scale	p-value
Gender (male = reference group)		769	14	1.85 (-1.58, 5.28)	0.291
CO (ppm)		485	9	0.31 (-0.18, 0.81)	0.211
PA level(inactive = reference group)		536	9	0.27 (-7.21, 7.76)	0.943
FTCD		869	17	0.23 (-0.57, 1.03)	0.571
Abstinence period (hours)		504	9	0.06 (-0.26, 0.37)	0.732
Baseline FS[1]		378	8	-0.52 (-1.84, 0.81)	0.443
Baseline FAS[1]		378	8	0.72 (-1.35, 2.80)	0.495
Resting heart rate (bpm)		462	9	0.22 (-0.01, 0.45)	0.062
Smoking years		502	10	-0.36 (-0.57, -0.16)	0.001
BMI (kg/m^2)		574	10	0.93 (0.36, 1.50)	0.001
Age (years)		796	15	-0.30 (-0.49, -0.10)	0.003
BMI & age	BMI	574	10	1.10 (0.52, 1.68)	
	Age			-0.27 (-0.51, -0.03)	

Notes: Each covariate is fitted individually with intervention (adjusted for study) in one-stage IPD meta-analyses. The results of the most appropriate model, including age and BMI in the same analysis, are also included; DtS substituted by SoD where no DtS scores were available, 1 = the combined cravings measure consists of DtS only. BMI = body mass index; FAS = felt arousal scale; FS = feeling scale; FTCD = Fagerström Test of Cigarette Dependence.

6.3.4 One-stage individual participant Data meta-analyses of physical activity on affect

Eight studies provided IPD for FS and FAS data (Haasova et al. unpublished; Janse Van Rensburg et al. 2009a; Janse Van Rensburg et al. 2009b; Janse Van Rensburg and Taylor 2008; Scerbo et al. 2010; Taylor and Katomeri 2007; Taylor et al. 2005). The effects of acute PA on FS and FAS were quantified using the extrapolated 0–100 scale. One-stage IPD analyses of post-intervention FS (372 observations) with random effects on the intervention and a fixed effect on study, and adjusted for baseline FS, yielded a mean difference of 7.30 (95% CI: 2.64 to 11.97) between the intervention group and controls, with an SD of 3.78 and 95% midrange of intervention effects across studies of -0.06; 14.66. Using the same approach, analyses of post-intervention FAS (372 observations) yielded a mean difference of 16.43 (95% CI: 7.53 to 25.34), with an SD of 8.16 and 95% midrange of intervention effects across studies of 0.43; 32.43. Results suggest that acute PA increases both affect measures, FS and FAS, among temporarily abstaining smokers. The results of these analyses were shown in **Table 19**, with the results on the original FS and FAS scales added. The effects were also quantified using moderate PA only, and similar results were found (**Table 19**). In addition, **Table 19** enables comparison of the effects of PA on affect with the effects of PA on cigarette cravings.

6.3.5 Change in affect as a potential mediator of the effect of physical activity on cigarette cravings

The potential mediating effects of change in FS and FAS on the observed reduction in cravings associated with PA were examined using only DtS as the cigarette cravings measure; all studies that collected affect data also used DtS as their cigarette cravings measure. Analyses of the effect of intervention on post-intervention DtS, with adjustment for baseline DtS, showed no significant association with change in affect when measured using FS or FAS. These findings suggest that neither FS nor FAS mediates the effect of PA on cigarette cravings as measured using DtS (**Table 21**). Sensitivity analyses, an analysis of moderate intensity PA only (**Table 21**) and an analysis using SoD as the cravings measure, showed similar results (Appendix F **Table 62** and **Table 63** respectively).

Table 21. Associations of change in affect (FS/FAS) and the effects of physical activity on cigarette cravings, using separate one-stage IPD meta-analyses for each covariate

Covariates	Number of observations	Number of studies	Mean difference (95%CI)	p-value
Change in FS	372	8	-0.13 (-0.29, 0.02)	0.091
Change in FAS	372	8	0.07 (-0.04, 0.18)	0.196
Change in FS (moderate intensity PA only)	318	8	-0.13 (-0.32, 0.05)	0.165
Change in FAS (moderate intensity PA only)	319	8	0.09 (-0.04, 0.21)	0.174

Notes: The combined cravings measure consists of DtS only (no SoD was available) in the analyses of affect. The included studies were: Haasova et al., unpublished; Janse Van Rensburg et al, 2009b; Janse Van Rensburg & Taylor, 2008; Katomeri, unpublished; Oh, & Taylor, 2014; Scerbo et al., 2010; Taylor & Katomeri, 2007; Taylor et al., 2005. DtS = desire to smoke; FAS = felt arousal scale; FS = feeling scale; PA = physical activity.

6.3.6 Physical activity attributes

The available combinations of the PA characteristics were presented in **Table 17**. Individually, all three attributes of PA, duration, intensity and type, were found to be significantly associated with a reduction in cravings (**Table 22**).

Table 22. The effects of physical activity attributes on cigarette cravings: separate one- stage meta-analyses of the effects of duration, type and intensity

PA characteristics (n)	Categories	Mean difference (95%CI) 0-100 scale	p-value
Duration (930)	Short	-12.73 (-35.91, 10.44)	0.282
	Medium	-31.12 (-45.74, -16.51)	< 0.001
	Long	-36.54 (-46.28, -26.81)	< 0.001
Type (930)	Isometric	-5.89 (-13.06, 1.28)	0.107
	Walking/running	-34.58 (-47.31, -21.85)	< 0.001
	Cycling	-35.53 (-45.81, -25.25)	< 0.001
Intensity (930)	Light	-9.22 (-15.24, -3.20)	0.003
	Moderate	-34.57 (-42.64, -26.50)	< 0.001
	Vigorous	-31.29 (-38.00, -24.57)	< 0.001

Notes: One-stage IPD meta-analyses (adjusted for baseline cravings), with a fixed effect on study, random intercept on participant, comparing PA categories against control participants. DtS was substituted by SoD where no DtS scores were available. Models had random effects applied on short, medium and long duration, walking/running and cycling (type), and moderate intensity categories. Negative ES for cravings measures favours intervention, and positive ES favours control condition. CI = confidence interval; n = number of observations; IPD = individual participant data; PA = physical activity.

Interventions of medium and long duration significantly reduced cigarette cravings in comparison with controls, as did walking/running and cycling interventions. Light, moderate and vigorous intensity interventions all significantly reduced cigarette cravings in comparison with controls. However, in a model including all three PA attributes (duration, intensity and type), only

the intensity of PA remained significant. In the final model, the moderate intensity effect was allowed to vary across studies, while a fixed effect was applied to the light and vigorous intensity PA categories (due to negligible variation in effect across studies or a very wide 95% CI on the standard deviation). A one-stage IPD meta-analysis (930 observations) yielded a mean difference in cravings compared with controls of -9.22 (-5.24; -3.12) for light intensity, -34.57 (-42.64; -26.50) for moderate intensity and -31.29 (-38.00; -24.57) for vigorous intensity PA. Sensitivity analyses, separate analyses for DtS and SoD, yielded similar results (Appendix F **Table 65** and **Table 64**).

6.4 Discussion

Possibly of most clinical importance were the results of the various attributes of PA on cigarette cravings. As suggested in the previous review (Haasova et al. 2013; Chapter 5), the intensity characteristics of PA significantly influenced the cravings reduction. Light intensity PA yielded a mean difference in cigarette cravings of -9.22 (-5.24; -3.12), suggesting a small clinical effect on cravings. Moderate intensity PA yielded the highest mean difference in post-intervention cravings compared with controls -34.57 (-42.64; -26.50), suggesting that moderate intensity PA offers the largest benefits. Vigorous intensity PA yielded a mean difference in post-intervention cravings compared with controls of -31.29 (-38.00; -24.57), very similar to the mean difference seen for the moderate intensity PA. Therefore, from a clinical perspective, there appears to be no additional benefit in terms of decrease in cravings from vigorous exercise compared with moderate exercise. Overall, there is sound evidence to recommend short bouts of moderate intensity exercise to smokers as a means of reducing cigarette cravings. In addition, moderate intensity exercise may be easier to adopt and maintain than vigorous exercise for sedentary smokers (Everson et al. 2008). In addition, interventions of medium (10 minutes) and long duration (15 and more minutes) significantly reduced cigarette cravings in comparison with bouts of short duration (5 minutes), suggesting that 10-15 minutes bouts of any intensity PA could be recommended for acute cravings reduction. However, these findings are drawn from a population of acute studies with only temporary smoking abstinence and may therefore have limited clinical applicability for smoking cessation. Yet, the length of the abstinence period (2–

30 hours) was not found to influence the self-reported cigarette cravings, suggesting a perhaps wider application of these findings.

The current study is the first to inspect the relationship of two commonly used single-item measures of cigarette cravings, SoD and DtS. While the scales are semantically different, both measures were found to be highly correlated. A composite measure of cravings was used in the main analyses. Although there was a considerable degree of variation in baseline and in post-intervention correlation coefficients among the individual studies, sensitivity analyses, separate analyses for DtS and SoD, yielded similar results and confirmed the findings from the main analyses. In addition, the use of a single cravings measure, (instead of two separate outcomes) helped to simplify the interpretation of the results. Similarly to the recent meta-analysis of the two separate outcomes, PA of any form (compared with a passive control condition) was found to be associated with approximately 30% reduction in cigarette cravings using the combined measure of cravings.

Importantly, no moderators of the effects of PA on cigarette cravings were identified. Both age and BMI were significantly associated with cravings but such associations may not be clinically significant, and these factors did not moderate the effect of the PA. In summary, the effects of PA on cravings reduction appear robust across a range of potential demographic and smoking related covariates. This has both practice and research implications. In terms of practice, PA could be recommended to all smokers regardless of factors such

as age, gender, level of nicotine dependence, or BMI. Most of the primary studies used an overnight smoking abstinence period, three studies (Faulkner et al. 2010; Haasova et al. unpublished; Scerbo et al. 2010) required a minimum abstinence period of 3 hours and two studies used a period of 2 hours (Katomeri unpublished; Taylor and Katomeri 2007). In terms of research, for example, the fact that the length of abstinence did not moderate the effects of PA on cravings the effects of PA on cravings suggests that shorter abstinence periods could be used to recruit heavy smokers in future studies.

Based on Taylor and colleagues (2007) review a positive influence of PA on measures of affect was expected. This study quantified the acute effects of PA on affect (measured by FS and FAS) among temporarily abstaining smokers using IPD meta-analysis. However, these effects did not explain the effects of PA on cigarette cravings. Acute bouts of PA were found to be significantly associated with FAS and FS scores. After short bouts of exercise, positive feelings (FS) and the level of arousal (FAS) were increased. However, neither FS nor FAS appeared to mediate the relationship between PA and cigarette cravings. One explanation may be that the effects of PA on FS and FAS were fairly small. Due to different methodologies and populations, the comparison of our results with the findings from the meta-analyses investigating the effects of aerobic exercise on positive activated affect (Reed and Ones 2006) was not suitable. Smokers deprived from cigarettes may score lower at the baseline than a normal population, and therefore may show higher effects. Alternatively, the negative effects of smoking on the respiratory tract may result in adverse feelings, showing smaller effects; some studies indicated that inactive and

overweight participants experienced reduced pleasure following exercise (Ekkekakis et al. 2011). This is not to discount changes in affect as a possible mechanism for some abstaining smokers; a number of different mechanisms may be operating alone or in combination at different times for different people (Faulkner and Carless 2006). These possibilities warrant further investigation to identify how PA influences affect.

6.5 Conclusion

All intensities of PA were found to be helpful in decreasing acute cigarette cravings and could be used in smoking cessation. In addition, 10-15 minutes long bouts of any intensity PA appeared to offer increased benefit when compared to bouts of 5 minutes duration. However, intensity of PA was found to be the most important attribute of PA. Moderate intensity PA provided increased benefit when compared with light intensity PA, whereas vigorous intensity PA did not confer additional benefits compared with moderate PA. There is no evidence to suggest a mediating role of affect (as measured by FS and FAS), while none of the demographic, health-related or smoking related variables investigated here appeared to be moderators of the effects of PA. Moderate intensity PA (e.g. walking) could be recommended to all smokers attempting to quit. However, the application of the use of PA in smoking cessation and its effectiveness remains to be examined.

Chapter 7: How habitual physical activity and other individual characteristics are associated with cigarette cravings: An exploration of baseline measures from the Exercise Assisted Reduction then Stop smoking study

7.1 Introduction

It is well established that smokers tend to be less active. A recent review concluded that 60% of all included studies found a negative association between smoking and levels of PA (Kaczynski et al. 2008). Also, physically active smokers were found to be more likely to quit in the past year compared with inactive smokers (Deruiter et al. 2008). However, no studies investigating the relationship between habitual PA and cigarette cravings have been identified. Habitual PA may have an important role in suppressing the level of cravings. Studies have shown a strong acute effect of bouts of PA on cigarette cravings (Haasova et al. 2013; 2014; Roberts et al. 2012), and it may be that these effects accumulate. Two cravings states are well established, a cravings state (cravings "right now"), and a cravings trait (more stable cravings state; Tiffany and Wray 2012). It is possible that a similar two states exists for PA. Acute cravings may represent the "right now PA state", while habitual PA may represent the more stable PA trait state; both states may be associated with cigarette cravings.

The relationship between habitual levels of PA and cigarette cravings (trait cravings) in smokers is investigated in this chapter, as are additional predictors of cigarette cravings and moderators of the association between habitual levels of PA and cigarette cravings. In summary, the research questions explored in this chapter are:

- Is there an association between habitual levels of PA and general cigarette cravings in the past week in smokers?
- If an association between habitual levels of PA and cigarette cravings exists, what are the additional predictors of cigarette cravings?
- If an association between habitual levels of PA and cigarette cravings exists, are there any moderators?

This chapter aims to answer these questions by examining baseline cross-sectional data collected in the Exercise Assisted Reduction then Stop smoking study (EARS; Taylor et al. 2014)

7.2 Methods

The EARS smoking study was a pragmatic, two arm pilot randomised controlled trial comparing counselling on PA and smoking reduction (to cut down, then quit), with brief advice on quitting, among hard to reach smokers who did not wish to quit in the next month (see the study report for more details: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0008/98657/FullReport-hta18040.pdf). The study was funded by the Health Technology Assessment Programme. The primary clinical outcome was 4-weeks post quit expired air carbon monoxide (CO; ppm) confirmed abstinence. The study was granted ethical approval by the NHS National Research Ethics Service Committee in The South West; the protocol was registered on Health Technology Assessment website (http://www.hta.ac.uk/protocols/200700780002.pdf). Recruitment started in May 2011 and finished in March 2012. Data were collected at baseline and 4, 8 and 16 weeks post-baseline.

This chapter examines baseline data for all EARS participants irrespective of the trial randomisation, the intervention and control arm baseline data are pooled together. All outcomes assessed at baseline are listed in Appendix B **Table 45**. However, only measures considered in this chapter are described in detail.

Based on the results from the acute data (chapter 6), it was expected that moderate intensity PA would be the best predictor of cigarette cravings compared with other PA intensities. A recent study (Bloom et al. 2012)

suggested that the relationship between smoking and PA within smokers may differ by gender as a result of different motives for exercise. Prevalence rates of smoking and substance abuse were repeatedly found to be higher in the unemployed compared with the employed internationally (Henkel 2011). The author of this review recommended collecting employment status, gender, age and socioeconomic status data in substance use research (Henkel 2011). It may be the case, that the employment status and demographics data have an association with cigarette cravings, as well as with the proposed association between habitual levels of PA and cigarette cravings in the past week. Similarly, other phenomena of smoking cessation, mood changes and withdrawal symptoms, may be associated with cravings and could be moderators of the proposed relationship between PA and cravings. In addition, because of the association between smoking variables and cigarette cravings, it is reasonable to expect an association between smoking variables and the proposed relationship between PA and cravings. Finally, alcohol consumption is a behaviour often associated with smoking, especially in the unemployed (Henkel 2011), therefore the potential effects of alcohol variables on the relationship between PA levels and cigarette cravings were investigated.

7.2.1 Participants

Participants were eligible if they were over 18 years old, smoked at least ten cigarettes per day for at least two years, did not want to quit in the next month, were able to walk without stopping for at least 15 minutes, were registered with a GP, and did not wish to use nicotine replacement therapy to

reduce smoking. The study recruited 99 participants, all of whom had available baseline data.

7.2.2 Measures

Physical activity

The Seven-day PA recall questionnaire assessed self-reported PA (Blair et al. 1985). Data were collected for PA at three intensities: light, moderate and vigorous. Moderate and vigorous intensity PA was combined into one variable, "moderate and vigorous intensity physical activity" (MVPA), to enable a comparison with the Chief Medical Officer recommended weekly PA guidelines. In addition, daily energy expenditure (EE) was calculated from self-reported PA data (Blair et al. 1985).

Cravings measures

Participants answered two questions about their smoking urges. The Strength of Urge to smoke (SoU; West and Hajek 2004; West and Russell 1985) was assessed using the following question: "*How strong have the urges been to smoke this past wee*k?". In addition, smokers were asked about Time Spent with Urges in the past week (TSwU; West and Hajek 2004); "*How much of the time have you felt the urge to smoke in the past week?*". Both scales have a 1−6 point response range, where 1 is *not at all/no urges* and 6 relates to *all the time/extremely strong.* As specified in Chapter 2 (section 2.3 on page 42) this chapter reports on the association between habitual levels of PA and SoU

only. Similarly to the acute data in Chapters 5 and 6, all cigarette cravings responses (1–6 point scale) were linearly rescaled to a range of 0–100 to facilitate the use of linear regression and to assist with interpretation of the results (Lyratzopoulos et al. 2012).

Demographics and background measures

Participants reported how many cigarettes and grams (or ounces) of tobacco they smoked over the past week. The reported scores were converted into the overall equivalent number of cigarettes smoked per day using the following formula: one cigarette was assumed to include 0.45 grams of tobacco (Laugesen et al. 2009), for use in statistical analyses.

Withdrawal symptoms were assessed by the Mood and Physical Symptoms Scale (MPSS) questionnaire (West and Hajek 2004). Quality of life was assessed using the three-level European Quality of Life-5 Dimension questionnaire (EQ-5D-3L; Prieto and Sacristan 2004). In addition, an answer indicating “some problems” or “extreme problems” on the anxiety/depression dimension was considered as an indication of potential mental health issues; hence, a binary variable indicating the presence/absence of mental health issues was included. Subjective stress was assessed by Perceived Stress Scale (PSS; Cohen et al. 1983). See Appendix G **Table 66** for more details.

Participants’ nicotine dependence was assessed using the Fagerström Test for Cigarette Dependence (FTCD; Fagerström 2012; Heatherton et al.

1991). In addition, information on the age when participants started smoking was collected. Smoking satisfaction and psychological reward was assessed using the modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al. 2007). It was expected that pleasure derived from smoking may reduce with increased PA.

In addition, participants answered three questions related to the past week's alcohol consumption. The first question: *"How often do you have a drink containing alcohol*" (subsequently referred to as "*Alcohol drinking frequency*") was answered by all EARS participants. The following two questions were answered only by participants who reported that they drink at least once a month or more frequently. Thus, only 84 participants answered the following questions: "*How many drinks containing alcohol do you have on a typical day when you are drinking*" (subsequently referred to as "*Drinks on a typical day*") and "*How many drinks containing alcohol have you had in the past week*" (subsequently referred to as "*Drinks in the past week*"). The questions were adapted from The Alcohol Use Disorders Identification Test (AUDIT; Allen et al. 1997). Based on preliminary analyses (see Appendix G **Table 67**–**Table 71** for more details), participants were classified as "not drinking alcohol", "light/moderate drinkers", and "heavy drinkers" into a new three-level "*Alcohol consumption*" variable (N = 99); the "*Alcohol drinking frequency*" and "*Drinks on a typical day*" variables were combined.

7.2.3 Statistical analyses

Data were described using the mean and standard deviation (SD), the median and interquartile range (IQR), or proportions. Associations were investigated using Spearman and Pearson correlations (based on skewness and kurtosis normality tests), and linear regressions (performing a series of models, each one including an individual explanatory variable). Although technically ordinal variables, measures of cravings (rescaled to a 0–100 point scale) were treated as continuous variables. The regression coefficients represent the mean difference in cravings between the baseline category and the comparison category, e.g. for gender, it would represent the difference between male and females. For example, a mean difference of -10 would indicate that SoD was decreased by 10 percentage points in the comparison category compared with the baseline category.

Two alcohol consumption questions were answered only by participants reporting drinking alcohol (N = 84). If appropriate the analyses of potential moderators of SoU and additional predictors of the relationship between PA and SoU were divided into two sections. First, the three level "*Alcohol consumption*" variable was considered in the whole sample (N = 99). Subsequently, "*Drinks on a typical day*" and "*Drinks over the past week*" were considered in a sub-sample who reported alcohol consumption (N=84).

All statistical analyses were performed using Stata 13 and the significance threshold was set at 0.05 in all analyses. All analyses described in this section

are post hoc exploratory analyses. In many analyses multiple tests of the trial outcomes were performed. Therefore, all results reported in this chapter must be interpreted with caution.

The effects of physical activity on Strength of Urge

To answer the first research question, (i.e. whether an association between habitual levels of PA and cigarette cravings in smokers exists) a series of linear regression models were applied individually with minutes of each PA intensity, and total EE as predictors of SoU. The likelihood ratio test (LR test) was used to compare the fit of models (where one model is nested inside the other) to assess whether total EE, and minutes of light and vigorous PA intensity (if they were individually significantly associated with cravings) would improve the prediction of SoU in addition to moderate PA.

In order to answer the second research question, (i.e. what are the additional predictors of cigarette cravings) the following two steps were performed:

Step 1: Correlations between potential additional predictors and Strength of Urges

First, correlation analyses between the above specified variables (EQ-5D-3L, mental health, MPSS and PSS, number of cigarettes smoked per day, FTCD, age when participants started smoking, mCEQ, and alcohol

consumption variables) and SoU informed the choice of variables for the exploration of additional predictors of SoU.

Only variables that were found to be significantly correlated ($p < 0.05$) with SoU or approaching significance ($p < 0.1$), were included in further analyses. In addition, all binary outcomes (employment status, gender, meeting PA guidelines, and mental health), and the three levels "*Alcohol consumption*" variable were considered in further analyses.

Step 2: Predictors of Strength of Urges

To identify additional predictors, the associations between potential predictors (as identified in step 1) and SoU were investigated using a series of individual linear regression models. The analyses were repeated with all individual models adjusted for PA. All individually significant additional predictors (after adjusting for PA) identified in the individual regression models were combined in one model. All variables that were significantly associated with SoU in the individual regression models were also combined in a backward stepwise regression model. In addition, all individually significant variables were included in a backward stepwise regression model with the moderate intensity PA variable included as a predictor regardless of its contribution to the model. These models aimed to identify additional predictors of cigarette cravings, with and without adjustment for PA.

In order to answer the third research question, (i.e. are there any moderators of the PA and craving relationship) the next third step was followed:

Step 3: Moderators of the effects of physical activity on Strength of Urges

The analyses of individually significant predictors of SoU (after adjusting for PA) were extended by including interaction terms with PA. Individual models (i.e. each including only one potential moderator) with the potential moderator, PA and potential moderator/PA interaction were applied to the data. Only variables demonstrating a significant interaction with PA were considered to be moderating the effects of acute PA on cigarette cravings (Kraemer et al. 2002). If appropriate, all moderators identified in the individual regression models were combined in one model to identify all significant moderators of the relationship between PA and cravings. The LR test was used to compare the fit of models.

Finally, in order to identify the most appropriate model, all significant predictors and moderators were combined, and the Step 4 was followed:

Step 4: Combining additional predictors of Strength of Urges and moderators of the effect of moderate intensity physical activity on Strength of Urges

If appropriate, all significant predictors and moderators were combined in one model. The LR test was used to compare the fit of models (where one model is nested inside the other).

7.3 Results

Table 23 summarises demographic and background characteristics for the sample of 99 participants.

Table 23 Participants characteristics; demographic and background variables (N = 99)

Characteristics		Descriptives
Age (years)	Mean (SD) Median (IQR)	46.6 (11.3) 47.5 (38.3, 55.4)
EQ-5D-3L	Mean (SD) Median (IQR)	0.749 (0.275) 0.796 (0.725, 1)
PSS	Mean (SD) Median (IQR)	5.7 (4.1) 4 (2, 9)
MPSS (1−5 scale)	Mean (SD) Median (IQR)	2.5 (0.9) 2.3 (1.8, 3.1)
Cigarettes smoked per day	Mean (SD) Median (IQR)	21.6 (14.3) 19.1 (14.4, 24.4)
FTCD	Mean (SD) Median (IQR)	5.6 (2.0) 6.0 (4.0, 7.0)
Age when participants started smoking (years)	Mean (SD) Median (IQR)	14.7 (3.5) 14.0 (13.0, 16.0)
mCEQ satisfaction (1−7 scale)	Mean (SD) Median (IQR)	3.8 (.5) 3.7 (2.7, 4.7)
mCEQ reward (1−7 scale)	Mean (SD) Median (IQR)	3.3 (1.2) 3.2 (2.6, 4.2)
Gender	Male (%; n/N) Female (%; n/N)	43 (43/99) 57 (56/99)
Mental health[a]	Yes (%; n/N) No (%; n/N)	41 (41/99) 59 (58/99)
Employment status	Employed (%; n/N) Not employed (%; n/N)	55 (54/99) 45 (45/99)

Notes: [a] answered 'moderately' or 'extremely' anxious or depressed to item 5 of the EQ-5D-3L questionnaire; EQ-5D-3L = three level European Quality of Life-5 Dimension questionnaire; MPSS = Mood and Physical Symptoms Scale; FTCD = Fagerström Test for Cigarette Dependence; mCEQ =modified Cigarette Evaluation Questionnaire; PSS = Perceived Stress Scale; N = Number of participants; SD = standard deviation; IQR = inter-quartile range.

Most participants drank at least once a month or more frequently; **Table 24** summarises all alcohol outcomes and **Table 25** summarises PA and cigarette cravings data.

Table 24 Participants characteristics; alcohol variables

Characteristics	Descriptives
"Alcohol drinking frequency" (N = 99, 1−5 scale)	
Mean (SD)	2.9 (1.2)
Median (IQR)	3 (2, 4)
Proportions, (%; n/N):	
Never	15 (15/99)
Once a month or less	26 (26/99)
2−4 times a month	26 (26/99)
2−3 times a week	20 (20/99)
4 times a week or more	12 (12/99)
"Drinks on a typical day" (N = 84, 1−5 scale)	
Mean (SD)	2.6 (1.3)
Median (IQR)	2 (1, 4)
Proportions, (%; n/N):	
1 or 2 drinks	27 (23/84)
3 or 4 drinks	24 (20/84)
5 or 6 drinks	20 (17/84)
7 to 9 drinks	18 (15/85)
10 or more drinks	11 (9/84)
"Drinks over past week" (N = 84, 1−6 scale)	
Mean (SD)	3.4 (2.1)
Median (IQR)	3 (1, 6)
Proportions, (%; n/N):	
None	30 (25/84)
1 or 2	17 (14/84)
3 or 4 drinks	8 (7/84)
5 or 6 drinks	7 (6/84)
7 to 9 drinks	7 (6/85)
10 or more drinks	31 (26/84)

Notes: N = Number of participants; SD = standard deviation; IQR = inter-quartile range.

Table 25 Participants characteristics; physical activity and Strength of Urges (N = 99)

Characteristics		Descriptives
Minutes of light PA per day	Mean (SD) Median (IQR)	992.4 (139.4) 1020 (908.6, 1088.6)
Minutes of moderate PA per day	Mean (SD) Median (IQR)	70.3 (88.5) 45 (17.1, 77.1)
Minutes of vigorous PA per day	Mean (SD) Median (IQR)	2.8 (14.1) 0 (0, 0)
Minutes of MVPA per day [a]	Mean (SD) Median (IQR)	73.1 (91.1) 45 (17.1, 77.1)
Daily Energy Expenditure (kcal/kg)[b]	Mean (SD) Median (IQR)	36.05 (3.9) 34.9 (33.7, 36.8)
Met PA guidelines	Yes (%; n/N) No (%; n/N)	70 (68/98) 30 (30/98)
Strength of Urge (0–100 scale)	Mean (SD) Median (IQR)	53.1 (23.4) 60.0 (40, 60)
Strength of Urge (1–6 scale)	Mean (SD) Median (IQR)	2.7 (1.2) 3.0 (2, 3)

Notes: a = N = 98; b = N = 95; N = Number of participants; MET = Metabolic equivalent of Task; MVPA = Moderate and Vigorous Physical Activity; SD = standard deviation; IQR = inter-quartile range.

7.3.1 The effects of physical activity on Strength of Urge

Table 26 summarises the association between self-reported PA (minutes of daily light, moderate, vigorous and MVPA intensities and EE) data and SoU.

Minutes of light, moderate, and MVPA intensities, and daily EE significantly predicted SoU ($p < 0.05$). Light intensity PA was positively associated with SoU, whereas daily EE, moderate and MVPA intensities were negatively associated with SoU. Therefore, for an increase in moderate PA of 30 minutes per day (within the range of the observed data), a mean reduction in SoU of around 2.5% (30*-0.08) would be expected. Because only eight

participants reported exercising at vigorous intensity PA, the results for moderate and MVPA intensities were very similar. For an increase in MVPA of 30 minutes per day (within the range of the observed data), a mean reduction in SoU of around 2.4% (30*-0.079) would be expected (using a model with MVPA only).

Table 26 Strength of Urge; results of series of linear regression models including each physical activity variable individually (N = 99)

PA	Mean difference (95% CI)	F statistics (p)	R^2
Minutes of light PA per day[a]	0.05 (0.02; 0.09)	$F_{(1,93)}$= 9.80 (0.002)	8.6%
Minutes of moderate PA per day[b]	-0.08 (-0.13; -0.03)	$F_{(1,96)}$= 10.04 (0.002)	8.5%
Minutes of vigorous PA per day	-0.05 (-0.39; 0.28)	$F_{(1,97)}$= 0.10 (0.746)	-0.9%
Minutes of MVPA per day[b]	-0.08 (-0.13; -0.03)	$F_{(1,96)}$= 9.79 (0.002)	8.3%
Daily Energy Expenditure[a] (kcal/kg)	-1.60 (-2.77; -0.40)	$F_{(1,93)}$= 7.09 (0.009)	6.1%

Notes**:** a = N = 95; b = N = 98; Strength of Urge (0-100 scale); 95 % CI = 95% Confidence Interval; MVPA = Moderate and Vigorous Physical Activity; N = number of participants; PA = Physical Activity; R^2 adjusted R^2.

In the next step, it was explored whether adding either light intensity PA, or daily EE to a model with moderate intensity PA improves the prediction of SoU. MVPA was excluded from these analyses because of collinearity with moderate intensity PA. It was found that adding light intensity PA or daily EE into the model did not improve the prediction of SoU compared with the model including moderate intensity PA alone. The LR test used to compare the fit of the model including moderate intensity PA alone with a model including moderate and light intensity PA was not significant (LR = 1.74, p = 0.187). Similarly, the LR test used to compare the fit of a model including moderate intensity PA alone with a

model including moderate intensity PA and daily EE was not significant (LR = 0.76, p=0.384).

In summary, self-reported moderate intensity PA was found to be the strongest predictor of SoU. In light of these results, only self-reported moderate intensity PA was used in all further analyses (analyses of potential predictors of cigarette cravings and moderators of the effect of PA on SoU)

Table 27 Spearman correlations between background variables and Strength of Urges (N = 99)

Measure	Correlation coefficient	P-value
EQ-5D-3L	-0.23	0.024
PSS	0.19	0.064
MPSS* (1-5 scale)	0.33	0.001
mCEQ satisfaction*	0.11	0.293
mCEQ reward*	0.29	0.004
Cigarettes smoked per day	0.08	0.415
FTCD*	0.32	0.001
Age when participants started smoking (years)	-0.13	0.194
"*Alcohol drinking frequency*" (1−5 scale)	-0.23	0.022
"*Drinks on a typical day*" (1−5 scale)[b]	0.29	0.007
"*Drinks in the past week*") (1−6 scale)[b]	0.13	0.233

Notes: * Pearson correlation; ; a = answered 'moderately' or 'extremely' anxious or depressed to item 5 of the EQ-5D-3L questionnaire; b = N = 84; EQ-5D-3L = three level European Quality of Life-5 Dimension questionnaire; MPSS = Mood and Physical Symptoms Scale; N = Number of participants; PSS = Perceived Stress Scale; FTCD = Fagerström Test for Cigarette Dependence; mCEQ = modified Cigarette Evaluation Questionnaire; N = Number of participants.

Step 1: Correlations between background variables and Strength of Urges

The relationship between background variables and SoU are shown in **Table 27**. EQ-5D-3L, MPSS, FTCD, mCEQ reward, "A*lcohol drinking*

frequency" and "*Drinks on a typical day*" were significantly correlated with SoU, and the correlation between PSS and SoU approached statistical significance.

Step 2: Predictors of Strength of Urge

This section investigates the relationship between PA and cigarette cravings further by identifying additional predictors. The following variables: PSS, MPSS, FTCD, mCEQ reward, "*Alcohol consumption*", "*Drinks on a typical day*", and mental health were found to be individually significantly associated with SoU (Appendix G **Table 72**).

The same seven variables: PSS, MPSS, FTCD, mCEQ reward, "*Alcohol consumption*", "*Drinks on a typical day*", and mental health, remained significantly associated with SoU after adjusting for PA (**Table 28**). In addition, moderate intensity PA remained significant when adjusting for the individual variables in all individual models.

Table 28 Series of linear regression models investigating the effects of each potential additional predictor individually on strength of urges (adjusted for moderate intensity physical activity, N = 98)

Additional predictors				**Moderate PA**	
		Mean difference (95% CI)	t statistics (p)	Mean difference (95% CI)	t statistics (p)
EQ-5D-3L		-10.23 (-26.87; 6.41)	-1.22 (0.225)	-0.08 (-0.13; -0.02)	-2.89 (0.005)
PSS		1.09 (0.01; 2.18)	2.01 (0.048)	-0.08 (-0.13; -0.03)	-3.02 (0.003)
MPSS		8.16 (3.28; 13.04)	3.32 (0.009)	-0.08 (-0.12; -0.03)	-3.06 (0.003)
FTCD		3.21 (1.06; 5.36)	2.96 (0.004)	-0.07 (-0.12; -0.02)	-2.81 (0.006)
mCEQ reward		5.51 (1.98; 9.03)	3.10 (0.003)	-0.08 (-0.13; -0.03)	-3.29 (0.001)
"Alcohol consumption"[a]	Light/moderate drinkers	-25.36 (-37.08; -13.62)	-4.30 (< 0.001)	-0.077 (-0.12; -0.03)	-3.22 (0.002)
	Heavy drinkers	-10.19 (-23.51; 3.14)	-1.52 (0.132)		
	Global F statistic of the three levels alcohol consumption[b]			$F_{(2,94)}$= 11.43; p < 0.001	
*"Drinks on a typical day" **	3 or 4 drinks	2.58 (-10.08; 15.25)	0.41 (0.686)	-0.07 (-0.12; -0.02)	-2.61 (0.011)
	5 or 6 drinks	3.25 (-10.26; 16.75)	0.48 (0.634)		
	7 to 9 drinks	16.13 (2.40; 29.86)	2.34 (0.022)		
	10 or more drinks	18.32 (2.05; 34.59)	2.24 (0.028)		
	Global F statistic of the five levels alcohol consumption[b]			$F_{(4,77)}$= 2.37; p=0.060	
Employment status		5.89 (-3.40; 15.18)	1.26 (0.211)	-0.07 (-0.13; -0.02)	-2.80 (0.006)
Mental health		10.80 (1.691; 19.91)	2.32 (0.021)	-0.07 (-0.12; 0.02)	-2.77 (0.007)
Met PA guidelines		2.36 (-8.91; 13.63)	0.42 (0.678)	-0.09 (-0.15; -0.03)	-2.95 (0.004)
Gender		1.49 (-7.75; 10.73)	0.32 (0.750)	-0.08 (-0.13; -0.03)	-3.06 (0.003)

Notes: * = N = 83; a = "not drinking alcohol" (no alcohol consumption), "light/moderate drinkers" (consuming between 1 and 6 alcoholic drinks on a typical day), and "heavy drinkers" (consumed 7 or more alcoholic drinks on a typical day); b = p-values are derived from a Wald test; c = answered 'moderately' or 'extremely' anxious or depressed to item 5 of the EQ-5D-3L questionnaire; "not drinking alcohol" was the baseline category for "alcohol consumption"; drinking 1-2 drinks was the baseline category for "How many

drinks containing alcohol do you have"; "male" was the baseline category for gender; "employed" was the baseline category for employment status; "not meeting PA guidelines" was the baseline category for Met PA guidelines; "lack of anxiety" was the baseline category for mental health; BMI = body mass index (kg/m2); EQ-5D-3L = three level European Quality of Life-5 Dimension questionnaire; ES = effect size; FTCD = Fagerström Test for Cigarette Dependence; mCEQ = modified Cigarette Evaluation Questionnaire; MPSS = Mood and Physical Symptoms Scale; N = Number of participants; PA = physical activity; PSS = Perceived Stress Scale.

Predictors; multiple linear regression analyses using the whole sample

When all individually significant predictors and moderate PA were included in the same regression model with SoU, only moderate intensity PA, MPSS and *"Alcohol consumption"* remained significant with SoU ($p < 0.05$). When the backward stepwise regression model was applied (including moderate PA, PSS, MPSS, FTCD, mCEQ reward, "*Alcohol consumption*", and mental health), moderate intensity PA, MPSS and *"Alcohol consumption"* were included in the model (**Table 29**).

Table 29. Stepwise regression model showing the predictors of Strength of Urge (N=99)

		Mean difference (95%CI)	t statistics (p)
Moderate intensity PA (minutes per day)		-0.07 (-0.11; -0.03)	-3.14 (0.002)
"Alcohol consumption"[a]	Light/moderate drinkers	-23.46 (-34.66; -12.26)	-4.16 (< 0.001)
	Heavy drinkers	-8.07 (-20.81; 4.66)	-1.26 (0.211)
MPSS		7.42 (2.97; 11.86)	3.31 (0.001)
F statistic		$F_{(4,93)} = 12.45$; $p < 0.001$	
R^2		0.349	

Notes: Notes: a = "not drinking alcohol" (no alcohol consumption), "light/moderate drinkers" (consuming between 1 and 6 alcoholic drinks on a typical day), and "heavy drinkers" (consumed 7 or more alcoholic drinks on a typical day); moderate PA, PSS, MPSS, FTCD, mCEQ reward, "alcohol consumption", and mental health were included in the regression model; Repeating the backward stepwise regression model without the moderate intensity PA variable kept in resulted in the same model; "not drinking alcohol" was the baseline category for "alcohol consumption"; 95 % CI = 95% Confidence Interval; PA = Physical Activity.

Repeating the backward stepwise regression model with enforced inclusion of moderate intensity PA resulted in the same model. MPSS and *"Alcohol consumption"* were additional predictors (adjusted for moderate intensity PA) of SoU in the whole sample. Both an increase in moderate intensity PA, and an increase in "Alcohol consumption" were associated with a decrease in SoU, and an increase in MPSS was associated with an increase in SoU.

Predictors; multiple linear regression analyses using alcohol drinking sub-population

When all individually significant predictors and moderate PA were included in the same regression model, only moderate intensity PA remained a significant predictor with SoU (p = 0.012). When the backward stepwise regression model (including PSS, MPSS, FTCD, mCEQ reward, *"Drinks on a typical day*", mental health, and moderate PA) was applied, moderate intensity PA and mCEQ reward remained in the model (**Table 30**).

Table 30. Stepwise regression model showing the predictors of Strength of Urge (alcohol drinking participants only, N = 84)

	Mean difference (95%CI)	**t statistics (p)**
Moderate intensity PA (minutes per day)	-0.07 (-0.12; -0.02)	-2.77 (0.007)
mCEQ reward	5.44 (1.86; 9.03)	3.02 (0.003)
F statistic	$F_{(2,80)}$= 8.13; p < 0.001	
R^2	0.169	

Notes: Moderate PA, PSS, MPSS, FTCD, mCEQ reward, "How many drinks containing alcohol do you have on a typical day when you are drinking?", and mental health were included in the regression model; Repeating the backward stepwise regression model without the moderate intensity PA variable kept in resulted in the same model; 95 % CI = 95% Confidence Interval; PA = Physical Activity.

Repeating the backward stepwise regression model with enforced inclusion of moderate intensity PA resulted in the same model. Only mCEQ was found to be an additional predictor (adjusted for moderate intensity PA) of SoU in the sub-population of alcohol drinking participants. An increase in moderate intensity PA was associated with a decrease in SoU, and an increase in mCEQ was associated with an increase in SoU.

Step 3: Moderators of the effect of moderate intensity physical activity on Strength of Urge

The analyses of all individually significant predictors (as identified in **Table 28**) were extended by including interaction effects with PA to identify any potential moderators of the effect of PA on cravings. Four continuous variables (PSS, MPSS, FTCD and mCEQ reward) and three categorical variables (*"How many drinks containing alcohol do you have on a typical day when you are drinking?*", "*alcohol consumption*" and mental health) were investigated as potential moderators of the effects of PA on SoU. Each potential moderator and its interaction with physical activity were included in an individual model with physical activity. All significant moderators are reported below.

"*Alcohol consumption*" and *"How many drinks containing alcohol do you have on a typical day when you are drinking?*" were found to moderate the relationship between moderate intensity PA and SoU. The interaction term between "a*lcohol consumption*" (a categorical variable with three levels; N =

99), and minutes of moderate PA (a continuous variable), was significantly different from zero ($F_{(2,92)} = 5.51$, $p = 0.006$) overall (**Table 31**).

Table 31 Linear regression showing the three levels alcohol consumption moderator of Strength of Urge (adjusted for physical activity; in the whole population, N = 99)

		Mean difference (95%CI)	t statistics (p)
Moderate intensity PA (minutes per day)		-0.12 (-0.24; -0.01)	-2.13 (0.035)
Three levels alcohol consumption[a]	Light/moderate drinkers	-25.46 (-39.07; -11.85)	-3.71 (< 0.001)
	Heavy drinkers	-22.96 (-38.80; -7.11)	-2.88 (0.005)
PA/ three levels alcohol consumption	Interaction between moderate intensity PA and "light/moderate drinkers"	0.01 (-0.12; 0.14)	0.19 (0.853)
	Interaction between moderate intensity PA and "heavy drinkers"	0.19 (0.04; 0.34)	2.52 (< 0.001)
F statistic		$F_{(5,92)} = 9.90$; $p < 0.001$	
R^2		0.350	
Global F statistic of the three-level alcohol consumption[b]		$F_{(2,92)} = 7.05$; $p = 0.001$	
Global F statistic of the PA/ three levels alcohol consumption interaction[b]		$F_{(2,92)} = 5.51$; $p = 0.006$	

Notes: a = "not drinking alcohol" (no alcohol consumption), "light/moderate drinkers" (consuming between 1 and 6 alcoholic drinks on a typical day), and "heavy drinkers" (consumed 7 or more alcoholic drinks on a typical day); b = p-values are derived from a Wald test; "not drinking alcohol" was the baseline category for drinking alcohol; 95 % CI = 95% Confidence Interval; PA = Physical Activity

It appears that the "not drinking alcohol" subgroup reported higher cigarette cravings compared with "light/moderate drinkers" and "heavy drinkers" (**Figure 21)**; the global F statistic of the three levels alcohol consumption was statistically significant (**Table 31**). However, the moderating effects of alcohol

consumption on the relationship between moderate intensity PA and SoU suggests that both “not drinking alcohol” subgroup and “light/moderate drinkers” are associated with a decrease in cigarette cravings as minutes of moderate PA increases, while “heavy drinkers” are associated with an increase in cravings (**Figure 21**).

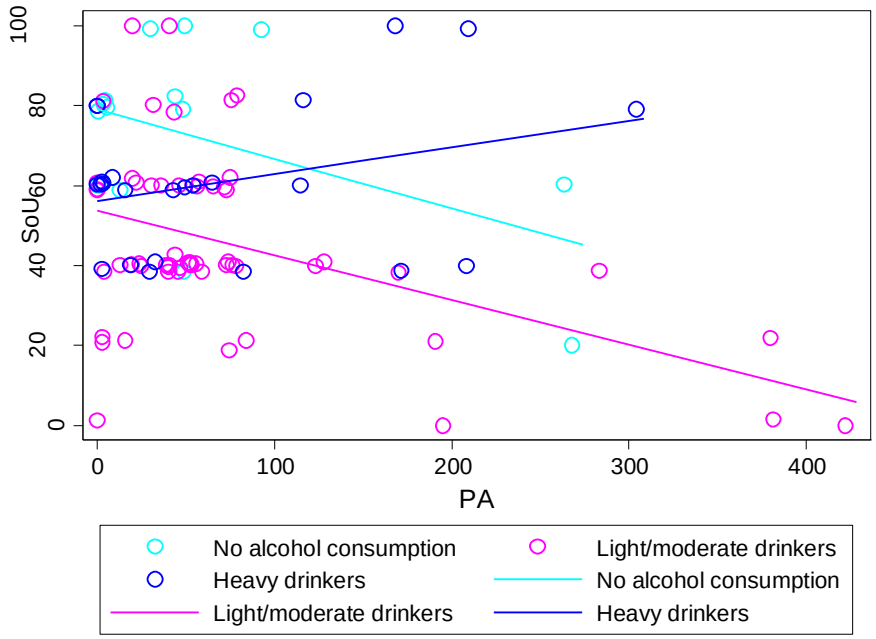


Figure 21 The relationship between “Alcohol consumption” and Strength of Urge in the whole population (N = 99)
Notes: PA = Physical Activity; SoU = Strength of Urges.

Similarly the interaction term between *“Drinks on a typical day?*” (a categorical variable with five levels, N = 84), and minutes of moderate PA (a continuous variable), was significantly different from zero ($F_{(4,73)}$ = 2.63, p = 0.041) overall (see Appendix G **Table 73** for more details).

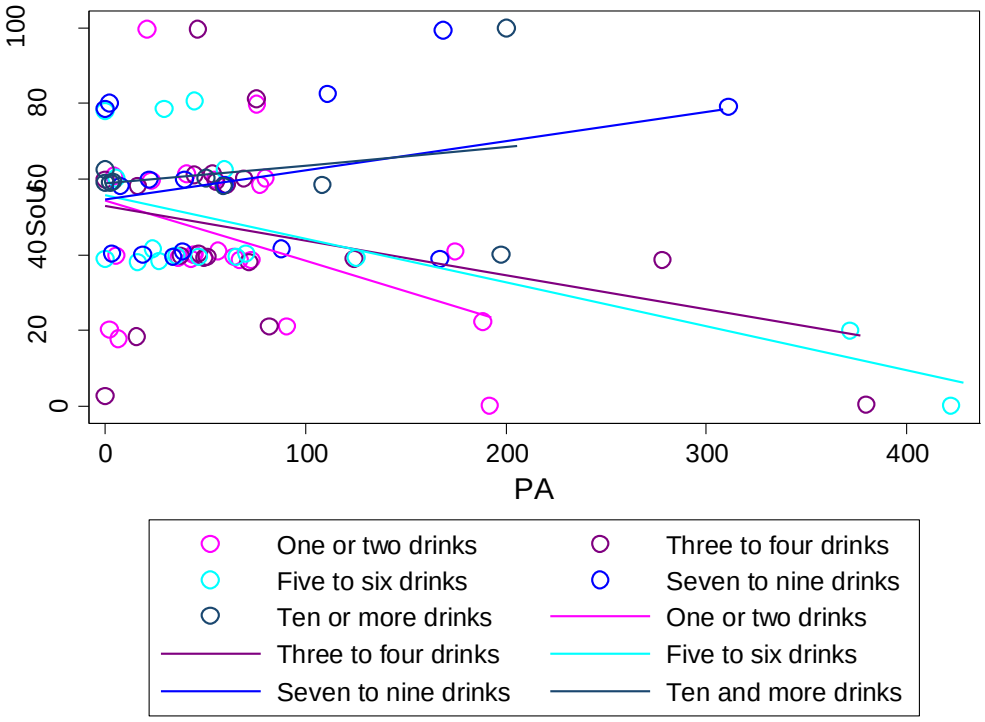


Figure 22 The relationship between "Drinks on a typical day" and Strength of Urge in alcohol drinking sub-population (N = 84)
Notes: PA = Physical Activity; SoU = Strength of Urges.

A decrease in cravings was associated with an increase in minutes of weekly moderate activity, overall. However, when the number of alcoholic drinks consumed on a typical day increased to seven or more, an increase of cigarette cravings was observed (**Figure 22**).

Step 4: Combining additional predictors of Strength of Urges and moderators of the effect of moderate intensity physical activity on Strength of Urges

All significant predictors and moderators were analysed together to identify the most appropriate model.

The most appropriate model, combined analyses using the whole sample

MPSS and "*Alcohol consumption"* were identified as additional predictors of the effects of PA on SoU*; "Alcohol consumption"* was also identified as a moderator of the effects of PA on SoU. The LR test was used to compare the fit of two models, the first including MPSS, PA, *"Alcohol consumption",* and the interaction between PA and *"Alcohol consumption"*, and the second (nested inside the first) excluding the interaction term.

Table 32. Strength of Urge; the most appropriate model in the whole population

		Mean difference (95%CI)	t statistics (p)
Moderate intensity PA (minutes per day)		-0.12 (-0.23; -0.01)	-2.16 (0.033)
Three levels alcohol consumption[a]	Light/moderate drinkers	-24.64 (-37.77; -11.46)	-3.72 (< 0.001)
	Heavy drinkers	-19.53 (-35.05; -4.07)	-2.51 (0.014)
PA/ three levels alcohol consumption	Interaction between moderate intensity PA and "light/moderate drinkers"	0.02 (-0.10; 0.15)	0.36 (0.720)
	Interaction between moderate intensity PA and "heavy drinkers"	0.67 (0.02; 0.31)	2.28 (0.028)
MPSS		6.18 (1.76; 10.59)	2.78 (0.007)
F statistic		$F_{(6,91)} = 10.13$; $p < 0.001$	
R^2		0.309	
Global F statistic of the three-level alcohol consumption[b]		$F_{(2,91)} = 6.91$; $p = 0.002$	
Global F statistic of the PA/ three levels alcohol consumption interaction[b]		$F_{(2,91)} = 3.93$; $p = 0.023$	

Notes: a = "not drinking alcohol" (no alcohol consumption), "light/moderate drinkers" (consuming between 1 and 6 alcoholic drinks on a typical day), and "heavy drinkers" (consumed 7 or more alcoholic drinks on a typical day); b = p-values are derived from a Wald test; "not drinking alcohol" was the baseline category for "*alcohol consumption*"; 95 % CI = 95% Confidence Interval; PA = Physical Activity; MPSS = Mood And Physical Symptoms Scale.

The LR test revealed that adding the interaction between PA and *"Alcohol consumption"* improved the model; LR = 8.12, p = 0.0173. Thus, the most appropriate model predicting SoU in the whole population includes PA, MPSS, *"Alcohol consumption"*, and the interaction between PA and *"Alcohol consumption"* (**Table 32**).

The most appropriate model, combined analyses using alcohol drinking sub-population

Table 33. Strength of Urge; the most appropriate model in alcohol drinking sub-population

		Mean difference (95%CI)	t statistics (p)
Moderate intensity PA (minutes per day)		-0.13 (-0.24; 0.02)	-1.74 (0.086)
"Drinks on a typical day"	PA/three to four	-0.04 (-16.88; 16.80)	-0.00 (0.996)
	PA/five to six	4.88 (-12.31; 22.07)	0.57 (0.573)
	PA/seven to nine	2.03 (-16.02; 20.07)	0.22 (0.823)
	PA/ten and more	3.97 (-17.10; 25.03)	0.38 (0.709)
PA /"Drinks on a typical day" interaction	PA/three to four	0.03 (-6.66; 5.27)	0.32 (0.752)
	PA/five to six	0.02 (-6.66; 5.27)	0.21 (0.833)
	PA/seven to nine	0.19 (-0.01; 0.38)	1.91 (0.06)
	PA/ten and more	0.19 (-0.03; 0.41)	1.69 (0.095)
mCEQ reward		4.46 (0.90; 8.02)	2.50 (0.014)
F statistic		$F_{(10,72)} = 3.66$; p = 0.001	
R^2		0.337	
Global F statistic of the five-level alcohol consumption[b]		$F_{(4,72)} = 0.13$; p = 0.970	
Global F statistic of the PA/ five level alcohol consumption interaction[b]		$F_{(4,72)} = 2.29$; p = 0.068	

Notes: a = participants responses were divided into the five following categories: one or two drinks, three or four drinks, five or six drinks, seven to nine drinks, ten or more drinks; b = p-values are derived from a Wald test; “one or two drinks” was the baseline category for “How many drinks containing alcohol do you have on a typical day when you are drinking?”; 95 % CI = 95% Confidence Interval; PA = Physical Activity

One additional predictor of the effects of PA on SoU was identified: mCEQ. In addition, a moderator of the relationship was identified: *“Drinks on a typical day”.* The LR test was used to compare the fit of two models, the first including mCEQ reward, PA, *“Drinks on a typical day”*, and the interaction between PA and *“Drinks on a typical day” and* the second (nested inside the first) excluding the interaction term and *“Drinks on a typical day”.*

The LR test revealed that adding the interaction between PA and *“Drinks on a typical day” and “Drinks on a typical day”* improved the model; LR = 18.74, p = 0.016. Thus, the most appropriate model predicting SoU in the alcohol drinking sub-population includes PA, mCEQ reward, and the interaction between PA and *“Drinks on a typical day”* (**Table 33**).

7.4 Discussion

This is the first study to indicate that habitual moderate intensity PA is associated with SoU over the past week. The more moderate intensity PA participants reported in the past week, the lower SoU was over the same period. This may either suggest that doing more PA will lead to lower cravings or those with lower cravings are likely to do more PA. It was suggested that smokers' cigarette cravings may be associated with levels of habitual PA simply because of the fact that active smokers smoke less compared with inactive smokers. This does not seem to apply to the EARS data. EARS participants were considerably active (70%, 68/98 met the Chief Medical Officer recommended weekly PA guidelines) and smoked a mean of 21 cigarettes (SD = 14.3) per day. In addition, neither FTCD nor number of cigarette smoked per day was found to be an additional predictor of SoU. It seems that the effects of habitual PA on trait cigarette cravings may be applicable to both light and heavy smokers.

Two additional predictors of SoU, MPSS and *"Alcohol consumption*", were identified (**Table 29**). Interestingly, comparing two types of participants, a light/moderate drinker and one not drinking alcohol (if all other variables remained constant), then the light/moderate drinker would rate his/her cravings 23 percentage points lower than the participant not drinking alcohol. Similarly, comparing a heavy drinker and a participant not drinking alcohol (if all other variables remained constant), then the heavy drinker would rate his/her cravings 8 percentage points lower than the participant not drinking alcohol

(**Table 29**). This difference between participants drinking and not drinking alcohol cannot be readily explained. One possible explanation may be that participants who also drink alcohol report lower cravings as their threshold for smoking is lower compared with participants not drinking alcohol; they light a cigarette at lower cravings compared with participants not drinking alcohol. Indeed, the "not drinking alcohol" subgroup reported higher cigarette cravings compared with "light/moderate drinkers" and "heavy drinkers" (**Figure 21**).

In addition, the three levels *"Alcohol consumption*" variable was found to moderate the relationship between moderate intensity PA and SoU (**Table 32**). The interactions revealed that "heavy drinkers" were associated with an increase in cravings as PA increased. It appeared that smokers consuming seven or more drinks per day on a typical day they drink lost the protective effect of habitual PA on SoU. However, as with all other findings in this chapter, it must be highlighted that EARS was designed as a pilot study and analyses presented here are post hoc exploratory analyses, thus the results must be interpreted with caution. In addition, the most appropriate model (described above; **Table 32**) explains only 35% of the variance in SoU, thus 65% of the variance remains unexplained.

Similarly, "*Drinks on a typical day"* was found to be a moderator in an alcohol drinking sub-population. A decrease in cravings was associated with an increase in minutes of weekly moderate activity, overall. However, when the number of alcoholic drinks consumed on a typical day increased to seven or

more, an increase of cigarette cravings was observed (**Figure 22**). A model including mCEQ (an additional predictor in this population), PA, *"Drinks on a typical day?"* and the PA/"*Drinks on a typical day"* interaction was identified to be the most appropriate model in this population. In this model, the interaction between PA and *"Drinks on a typical day*" explains the variability in the model better than PA on its own and as a consequence PA became non-significant in this model.

In summary, although an association between habitual PA and SoU was identified, the exact mechanism or mechanisms of the relationship remain unknown. However, it appears that not all physically active smokers are light smokers. A recent Cochrane review of the chronic effects of PA on smoking cessation identified 15 RCTs, however only one study (Marcus et al. 1999) showed long term benefit of exercise on smoking cessation (Ussher et al. 2012). The association between pre-quit cravings and cessation outcomes was questioned in a recent review (Wray et al. 2013). In addition, studies included in the Cochrane review studies did not aim to increase levels of habitual PA (Ussher et al. 2012). Further research exploring the association between habitual PA and cigarette cravings is needed. In addition, an investigation of the association between habitual PA and changes in habitual PA, and smoking outcomes is needed before a role of habitual PA smoking cessation can be established.

In addition, the *"Drinks on a typical day",* and *"Alcohol consumption"* variables identified to be moderators of the relationship between moderate intensity PA and SoU indicate only the frequency of alcohol consumption and pattern of drinking on a typical day. In contrast, overall alcohol consumption is a function of frequency of drinking in combination with number of drinks consumed on each day when drinking. Therefore, further research into the moderating effects of alcohol drinking, specifically the overall alcohol consumption, on the effects of habitual PA on cigarette cravings is warranted. From a clinical perspective, it is important to identify smokers who may not benefit from increasing of habitual levels of PA. Based on this study exploratory finding, clinicians should be cautious recommending increasing of habitual PA for reducing cigarette cravings among heavy drinkers.

7.5 Conclusion

Habitual PA was found to be significantly associated with SoU; an increase in moderate PA was associated with a decrease in SoU. Additional predictors of the effects of PA on SoU were identified. Moderate intensity PA was associated with SoU after controlling for MPSS and *"Alcohol consumption".* An increase in MPSS was associated with an increase in SoU, while an increase in *"Alcohol consumption"* was associated with a decrease of SoU. In addition, a moderation effect between moderate PA and *"Alcohol consumption"* was found. An increase in the number of minutes of moderate PA reduced cravings; however, at higher levels of alcohol consumption (seven or more drinks on a typical day when drinking), increased minutes of moderate PA appeared to be associated with increased cravings. It must be highlighted that all analyses in this chapter are exploratory and must be interpreted with caution.

Chapter 8: General Discussion and Conclusion

The first section of this chapter interprets and evaluates the results of the four studies included in this thesis (Chapters 4–7), and places these results in the context of the literature. The implications for future research are discussed in the second section and the strengths and weaknesses of the present research are summarised in the third section. Conclusions are drawn in the fourth section, and the final section summarises studies included in this research.

The aims were specified in Chapter 1, section 1.2 (p18); (I) to determine whether physical activity (PA) is more effective (compared with a passive condition) in reducing cigarette cravings among temporarily abstaining smokers, and whether there are any differences between the effects of walking and isometric (ISO) exercise; (II) to determine the effects of a short bout of PA on cigarette cravings among temporarily abstaining smokers using individual participants data (IPD) meta-analysis; (III) to determine who most benefits from PA and whether changes in affect mediate these effects, and whether any attributes of PA are associated with cigarette cravings among temporarily abstaining smokers; and (IV) to determine the effects of habitual PA on cigarette cravings in smokers.

8.1 Discussion

Systematic reviews found that short bouts of physical activity (PA) can acutely decrease cigarette cravings and withdrawal (Taylor et al. 2007; Ussher et al. 2012). In line with the evidence, Study 1 (Chapter 4) found beneficial effects of walking and ISO exercise on cigarette cravings and withdrawal. Cigarette cravings were assessed by two single-item measures: Desire to Smoke (DtS; Tiffany and Drobes 1991) and Strength of Desire to Smoke (SoD; West and Hajek 2004; West et al. 1989; West and Russell 1985). Withdrawal symptoms were assessed using the Mood and Physical Symptoms Scale (MPSS; West and Hajek 2004; West and Russell 1985). Study 1 concluded that smokers wishing to use PA as a smoking cessation aid may choose to use either walking or seated ISO exercise, depending on situational constraints and personal preferences. However, in contrast with the Janse Van Rensburg and colleagues (2009) study, no effects of PA on attentional bias (AB) was identified (Janse Van Rensburg et al. 2009a).

It appears that apart from the current study, there is only one other study investigating the effects of PA on AB in temporarily abstaining smokers (Janse Van Rensburg et al. 2009a), therefore more research is needed in this area. It was suggested that direct measures of AB (such as eye-tracking methods) in more real world settings are preferable (Ataya et al. 2012; Field and Christiansen 2012; Field et al. 2009a; Schmukle 2005). It is important to carefully consider the research question of each individual study and choose the appropriate design. For example, the design of Study 1 may have been too

complex to detect the effects of two different types of PA on AB even if they existed. Study 1 attempted to answer Aim I of this thesis. However, the results of the study highlighted the limitation of small acute studies trying to answer several research questions (Button et al. 2013).

IPD meta-analysis, although time-consuming, offers the most appropriate means of combining data from randomised controlled trials (Lyman and Kuderer 2005; Riley et al. 2011; Stewart and Clarke 1995). Thus, following a systematic review of the literature, Study 2 (Chapter 5) quantified the acute effects of PA on cigarette cravings using IPD meta-analyses. Nineteen studies examining the effects of acute PA on either SoD or DtS (assessed on a 1–7 point Likert scale) were included in the review; 15 studies reported SoD and 17 studies reported DtS. All analyses (including sensitivity analyses), suggested a decrease in cigarette cravings post exercise compared with a control condition. The magnitude of the cravings reduction was comparable with and exceeded the cravings reduction associated with glucose, and nicotine replacement therapy (Cahill et al. 2012; Taylor et al. 2007). The results found in Study 2 were similar to those of two aggregate data meta-analyses, one reporting SoD, including nine studies, and one reporting DtS, including ten studies (Roberts et al. 2012). The similarity of results derived from these meta-analyses (Haasova et al. 2013; Roberts et al. 2012) suggests that the effects of PA on acute cigarette cravings are robust. Study 2 answered Aim II of this thesis; the effects of short bouts of PA on cigarette cravings among temporarily abstaining smokers were determined. However, Study 2 also raised further questions.

Study 3 (Chapter 6) attempted to answer these questions. Potential predictors, moderators and mediators (changes in positive feelings and the level of arousal) of the effects of PA on cigarette cravings, and the effects of specific features of PA (such as type, intensity or duration) on cigarette cravings among temporarily abstaining smokers were investigated. The two cravings measures, SoD and DtS, were found to be correlated and a composite measure of cravings was used instead. In addition, to further the ease of interpretation of the results, all responses were linearly rescaled to a range of 0–100 (Lyratzopoulos et al. 2012).

Study 3 identified the intensity of PA to be the most important attribute of PA with regard to association with cigarette cravings post-intervention. All intensities of PA were found to be helpful in decreasing acute cigarette cravings. From a clinical perspective, there appeared to be no additional benefit in terms of decrease in cravings from vigorous PA compared with moderate PA. Incidentally, moderate intensity exercise was suggested to be easier to adopt and maintain than vigorous exercise by sedentary smokers (Everson et al. 2008). No moderators of the effects of PA on cigarette cravings were identified. No evidence was found to indicate that affect was a mediator of the relationship between PA and cigarette cravings. Study 3 attempted to answer Aim III of this thesis. Based on the evidence of Study 3, moderate intensity PA (e.g. walking) could be recommended as a cessation aid to smokers. No evidence was found to indicate that moderate PA would have differential effects across different characteristics such as age, gender, level of nicotine dependence, or body mass index.

New studies supporting the results have been identified since publishing Study 2 and 3. One study compared mild-to-moderate intensity walking with a passive condition (watching a gardening video) and found a decrease in SoD in temporarily abstaining pregnant smokers (Prapavessis et al. 2014). Similarly, a decrease in SoD was found in temporarily abstaining smokers who were also exposed to an environmental manipulation with two concurrent stressors (Stroop task and cue-elicited smoking stimuli) after a moderate intensity walking condition compared with a passive sitting condition (Fong et al. 2014). A decrease in DtS was found in temporarily abstaining smokers following a moderate intensity walking compared with a passive sitting condition (Schneider et al. 2014). Beneficial effects of low and moderate intensity PA on QSU-brief compared with a passive control condition in temporarily abstaining smokers were reported (Kurti and Dallery 2014). Finally, one study did not identify significant effects of PA on DtS compared with a passive condition (listening to a script describing activities of daily living, e.g. making dinner or getting ready for bed) and an exercise imaginary condition (listening to an audio script; Cooke et al. 2014). Instead, Cooke and colleagues (2014) reported a significant decrease in cigarette cravings in all three conditions post intervention (Cooke et al. 2014). The authors postulated that the control condition may have had relaxing effects (e.g., listening to the script and imagining themselves preparing to go to bed) on the participants (Cooke et al. 2014).

The exact mechanisms behind the effects of PA on cigarette cravings remain unknown. Expectation, changes in affect, and distraction are some of the proposed mechanisms causing the effects of PA on cigarette cravings

(Taylor et al. 2007). Individual studies tend to report increases in positive affect following PA in temporarily abstaining smokers (e.g. Daniel et al. 2006; Taylor et al. 2006). An indication of an increase in positive affect (Hardy and Rejeski 1989) following 10 min of walking was also observed in Study 1 (Chapter 4). Interestingly, one study found an increase in negative affect following moderate intensity PA in temporarily abstaining adolescent smokers (Everson et al. 2006). An association between changes in mood and cravings was identified, however changes in affect did not mediate the relationship between PA and cigarette cravings among temporarily abstaining smokers (Chapter 6; Haasova et al. 2014). It was suggested that a number of different mechanisms may be operating alone or in combination at different times for different people, therefore affect could be a possible mechanism for some abstaining smokers (Faulkner and Carless 2006).

The main research question of the Daniel and colleagues (2006) study was to examine whether distraction could be the mechanism behind the effects of PA on cigarette cravings (Daniel et al. 2006). Participants were randomised to cycling condition or control condition with a distraction counting task. Because a decrease in cravings was observed in the cycling condition only the authors concluded that distraction is not the mechanism causing the effects of PA on cigarette cravings (Daniel et al. 2006). Similarly, Taylor and Katomeri (2007) concluded that the effects of PA on cigarette cravings are unlikely to be caused by distraction (Taylor and Katomeri 2007). In this study, participants were randomised to a brisk walk or passive control condition. Following the intervention participants completed two mentally demanding tasks (the Stroop

task and a speech task) and also handled a lit cigarette. Cravings were measured at baseline, mid and post treatment, pre and post each of the two tasks, and pre and post the lit cigarette. Walking was associated with a decrease in cravings post the lit cigarette compared to a control condition. In addition, in the walking condition cravings were lower compared with baseline at each time point; up to 50 minutes post exercise. The authors concluded that the effects of distraction are unlikely to last up to 50 minutes post exercise (of 15 min duration) and to extend through mentally demanding tasks and the presence of a lit cigarette (Taylor and Katomeri 2007).

One study investigated whether the effects of PA on cravings could be caused by the expectations participants may have from PA; participants were randomised into three conditions with positive, negative, and neutral statements about PA before engaging in 10 minutes of moderate intensity cycling (no passive control condition was included; Daniel et al. 2007). A decrease in cravings was observed in all three conditions following PA and the authors concluded that the effects of PA on cravings are not due to the participant's expectations from PA (Daniel et al. 2007).

Interestingly, similar effects in decreasing cigarette cravings were reported for body scanning techniques (Ussher et al. 2009; Ussher et al. 2006) and very low intensity PA such as ISO exercise (Study 1;Ussher et al. 2009; Ussher et al. 2006), and yoga (Elibero et al. 2011). It has been suggested that the decrease in cravings may be due to a decrease in stress (Taylor et al. 2007). One study observed a decrease in cigarette cravings following exercise imaginary and a passive condition and proposed that the effects could be due to relaxation

(Cooke et al. 2014). Non-active conditions, conditions with tasks controlling attention, such as body scanning or exercise imaginary seem to also some have effects on cigarette cravings. In addition, it has been suggested that moderate intensity PA may reduce cigarette cravings by shifting brain activation away from areas associated with cravings (Janse Van Rensburg et al. 2009b). Participants were randomised to a cycling or passive control condition; following treatments participants viewed a series of smoking and neutral images in a functional Magnetic Resonance Imagining scanner. While participants in the control condition showed activation in areas associated with reward, motivation and visual-spatial attention, participants in the exercise condition showed hypo-activation in these areas (Janse Van Rensburg et al. 2009b). These finding were confirmed in a similar study using a more robust design of series of blocks of smoking and neutral images (Janse Van Rensburg et al. 2012).

It seems that although the mechanism behind the effects of PA on cigarette cravings is unknown, it seems reasonable to suggest that it will likely be a combination of mechanisms. In addition, it may be that different mechanisms will apply for different people in different situations. The variability of effects of vigorous intensity PA on affect has been well documented (e.g. Ekkekakis et al. 2011). A similar variability may exist for the mechanisms behind the effects of PA on cigarette cravings. The findings from Study 3 and Study 4 suggesting no added benefit to vigorous intensity PA compared with moderate intensity PA in decreasing cigarette cravings are in support of the above proposed mechanisms, e.i. relaxation, distraction and mood changes. However, the fact that non-active conditions are associated with a lesser decrease in cravings

compared with moderate intensity PA may suggest an existence of a mechanism unique to PA.

Because results of Study 2 and Study 3 were drawn from a population of acute studies with only temporary smoking abstinence and with a limited clinical applicability for smoking cessation, Study 4 (Chapter 7) examined the effects of habitual PA on cigarette cravings in smokers attempting to reduce smoking. The association between habitual levels of PA (over the past week) and cigarette cravings (SoU over the past week) were explored. Based on the results from Study 3, it was expected that moderate intensity PA would be the best predictor of cigarette cravings. Similarly to Study 2 and 3, all cravings responses were linearly rescaled to a range of 0–100 (Lyratzopoulos et al. 2012).

Study 4 results were similar to the acute data (Study 2 and 3), where both moderate and vigorous intensity PA reduced cravings, but vigorous intensity PA did not confer any extra benefits. Although both moderate and vigorous intensity PA was associated with SoU, moderate intensity PA was identified to be the best predictor of SoU. However, it must be highlighted that only eight participants (8/99) reported vigorous intensity PA in Study 4. An increase in habitual moderate PA of 5–40 minutes per day (within the range of the observed data), was associated with a mean reduction in SoU of around 0.4–3.3%. The effects of habitual moderate PA appeared to be much smaller when compared with the acute data. In comparison, Study 2 suggested an approximate cravings reduction of 30% associated with acute bouts of PA

lasting from 5–40 minutes. The results suggest that smokers attempting to quit or reduce smoking could benefit from acute PA.

In addition, MPSS was identified to be an additional predictor of SoU, and alcohol consumption was found to moderate the effects of habitual PA on SoU in Study 4. An increase in withdrawal (MPSS) was associated with an increase in SoU, while an increase in alcohol consumption was associated with a decrease in SoU. There was evidence to indicate an interaction between alcohol consumption and levels of habitual PA; heavier consumption (consuming seven or more drinks per day on a typical day they drink) was associated with higher cravings as minutes of moderate PA increased, whereas light/moderate consumption (consuming 1–6 drinks on a typical day drinking) and non-consumption of alcohol were associated with lower cravings as minutes of moderate PA increased. However, these results are only exploratory. Although Study 4 did not determine the effects of habitual PA on trait cravings in smokers, the exploratory analyses suggested that habitual PA is associated with trait cravings in smokers. The effects of acute PA on cigarette cravings have been quantified among temporarily abstaining smokers, and similar, although much smaller, effects were suggested for habitual PA and trait cigarette cravings. In agreement, both the acute studies and the exploratory study in smokers found that moderate intensity PA is the strongest predictor of cigarette cravings.

8.2 Strengths and limitations of the research

A strength of this thesis is that it includes analyses of both primary and secondary data. The weakness of the acute study is that it employed a very complicated design. However, this only highlighted the need for evidence synthesis and the option of exploring the use of secondary data to answer a specific research question. A strength of this research is the identification of all studies published up until May 2011 (searches finished on 31st May 2011) investigating the effects of PA on cigarette cravings, quantifying these effects, investigating potential effect modifiers using rigorous statistical approaches with IPD and publishing the data (Haasova et al. 2013; 2014). Recent studies generally support the findings from Study 1 – 3 (Cooke et al. 2014; De Jesus et al. unpublished; Fong et al. 2014; Kurti and Dallery 2014; Prapavessis et al. 2014; Schneider et al. 2014).

The main limitation of the research is that, although the effects of PA on cigarette cravings among temporarily abstaining smokers were quantified, the applicability of these effects to smokers attempting to quit is limited. Although the role of cravings in smoking cessation is still being debated (Tiffany and Wray 2012), cravings cause discomfort to smokers trying to reduce or quit smoking and have a key role in tobacco addiction. There is some evidence that a third of ex-smokers experience some urges even one year after they stopped smoking (Ussher et al. 2013). Therefore a relief of 30% in acute cravings after a short bout of PA is an important finding (Chapter 2–3). Acute PA may have an important role in smoking cessation trials (Abrantes et al. unpublished).

Another limitation is the number of cigarette craving measures used by researchers in this area. It would be useful if only one measure of cravings was endorsed and used in this research area. Incidentally, the Russell standard criteria applicable to smoking cessation trials did not recommend measurement of cigarette cravings (West et al. 2005).

8.3 Implications for future research

Although the mechanisms behind the effects of PA on cigarette cravings are unknown, the research contained within this thesis provides valuable information about the effects of acute PA on cigarette cravings among temporarily abstaining smokers. This information is critical for incorporating PA into smoking cessation interventions. PA is an important health behaviour and the use of PA in smoking cessation may have significant implications on other health outcomes. It is imperative to find out if the effects identified in acute data among temporarily abstaining smokers (Studies 1–3) translate to habitual PA and trait cigarette cravings in smokers trying to quit or reduce smoking. Study 4 suggested that these effects may exist. However, the associations between habitual PA and cravings (and other smoking outcomes) need to be explored before the role of habitual PA in smoking cessation can be fully established.

A recent Cochrane review of chronic effects of PA on smoking cessation identified 15 randomised control studies, however only one study (Marcus et al. 1999) showed a long-term benefit of exercise on smoking cessation (Ussher et al. 2012). It must be highlighted that the studies included in the review did not aim to increase levels of habitual PA (Ussher et al. 2012). The roles of acute and habitual PA in cravings reduction among smokers trying to quit or reduce smoking needs to be further investigated.

In addition, further research into the moderating effects of alcohol consumption, specifically the overall alcohol consumption, on the effects of

habitual PA on cigarette cravings is necessary. Based on the results of Study 4 (Chapter 7) there was some evidence to indicate higher cravings in heavier alcohol drinkers who also completed higher levels of moderate PA.

Finally, the different results of the two studies investigating the effects of PA on AB suggest that more research in the effects of PA on AB is needed (Haasova et al. unpublished; Janse Van Rensburg et al. 2009a).

In summary, further research should try to answer the following questions:

- What are the effects of habitual PA on trait cigarette cravings in smokers?
- Is there a moderating effect of alcohol usage, specifically the overall alcohol consumption, on the effects of habitual PA on trait cigarette cravings?
- What are the effects of acute PA on AB in smokers?

8.4 Conclusion

The effects of acute PA on cigarette cravings among temporarily abstaining smokers are large; 30% decrease in craving was identified. All intensities of PA were found to be helpful in decreasing acute cigarette cravings and could be used in smoking cessation. Moderate intensity PA provided increased benefit when compared with light intensity PA, whereas vigorous intensity PA did not confer additional benefits compared with moderate PA. In addition, evidence suggests that similar although smaller effects may exist between habitual PA and trait cravings in smokers. Moderate intensity PA (e.g. walking) could be recommended to all smokers attempting to quit. However, the application of the use of PA in smoking cessation and its effectiveness remains to be examined. The role of alcohol consumption on the effects of habitual PA on trait cigarette cravings requires further investigation.

8.5 Summary of studies

This section provides a brief summary of the four studies that informed this research.

Study 1: The effects of brisk walking and seated isometric exercise on cigarette cravings and attentional bias to smoking cues.

Chapter 4 investigated the effects of brisk walking and seated isometric (ISO) exercise on cigarette cravings: Desire to Smoke (DtS; Tiffany and Drobes 1991) and Strength of Desire to Smoke (SoD; West and Hajek 2004; West et al. 1989; West and Russell 1985), and withdrawal: Mood and Physical Symptoms Scale (MPSS; West and Hajek 2004; West and Russell 1985) in comparison to a rest condition in a group of temporarily abstaining smokers. In addition, attentional bias (AB) toward smoking cues was measured directly, using eye-tracking and indirectly, using a reaction time AB score from a probe task. The results of this study suggested that both modes of physical activity, walking and ISO exercise, had a similar effect on cigarette cravings and withdrawal. No effect of PA on AB data was found. However, the low statistical power of similar size studies (N = 20) and the increase in numbers of new studies investigating the effects of acute physical activity (Ussher et al. 2012), highlighted a need for a systematic review of studies investigating the effects of physical activity on cigarette cravings among temporarily abstaining smokers. The results were presented in Cardiff in 2011 (Haasova et al. unpublished) at Action on Smoking and Health (ASH) Wales conference; Appendix A **Figure 23**).

Study 2: The acute effects of physical activity on cigarette cravings: Systematic review and individual participant data meta-analysis.

Chapter 5 examined the effects of PA on cigarette cravings in temporarily abstaining smokers. A systematic review of literature was conducted and the identified studies were summarised using individual participant data (IPD) meta-analyses. This is the first study to quantify the acute effects of PA on cigarette cravings using IPD meta-analysis. Using two 1–7 point cigarette cravings scales, desire to smoke and strength of desire to smoke, a decrease of approximately 30% in cigarette cravings was found in participants engaging in physical activity compared with a passive condition. This review highlights the potential of a single session of PA to reduce cravings. The results of this chapter were presented at The European College of Sport Science (ECSS) conference in Liverpool, UK in 2012 (Appendix A **Figure 24**) and published (Haasova et al. 2013; Appendix A page 200). However, although the effects of physical activity on cigarette cravings in temporarily abstaining smokers were quantified, the study raised the following further questions:

- Are there any potential predictors of cigarette cravings post-intervention, or moderators of the effect of physical activity on cigarette cravings?
- Is it possible to identify any mediating mechanisms by which physical activity influences cigarette cravings (e.g. affective activation or valence)?
- Are there any specific features of physical activity (such as type, intensity or duration) that have differential effects on cigarette cravings?

Study 3: The acute effects of physical activity on cigarette cravings: Exploration of potential moderators, mediators and physical activity attributes using systematic review and individual participant data meta-analyses.

Chapter 6 investigated who most benefits from PA, whether changes in affect mediate these effects, and whether specific attributes of PA are associated with cigarette cravings. The individual participant data from randomised controlled trials collated in Study 2 were utilised. This chapter attempts to answer the questions raised in Study 2 using multilevel modelling. The results suggest that intensity of physical activity is the most important attribute of physical activity. All intensities of physical activity were found to be helpful in decreasing cigarette cravings in temporarily abstaining smokers. Moderate intensity PA provided increased benefit when compared with light intensity PA, whereas vigorous intensity PA did not confer additional benefits compared with moderate PA. In addition, 10-15 minutes long bouts of any intensity PA appeared to offer increased benefit when compared to bouts of 5 minutes duration. There was no evidence to suggest a mediating role of affect (as measured by FS and FAS), while no moderators of the effects of PA were found. The results of this chapter were published (Haasova et al. 2014; Appendix A page 201) and presented at The Society for Research on Nicotine and Tobacco (SRNT) conference in Boston, USA in 2013 (Appendix A **Figure 25**). Based on the results, moderate intensity PA (e.g. walking) could be recommended to all smokers attempting to quit. However, further investigation is required regarding the application and effectiveness of the use of physical activity in smoking cessation.

Study 4: How habitual physical activity and other individual characteristics influence cigarette cravings: An exploration of baseline measures from the Exercise Assisted Reduction then Stop smoking study.

Chapter 7 investigates the effects of habitual PA on cigarette cravings in smokers who are not temporarily abstaining from cigarettes. Smoking, affective and demographic variables were considered to be additional potential predictors of cigarette cravings, as well as moderators of the relationship between PA and cigarette cravings. Habitual PA was found to be significantly associated with SoU, with moderate PA being the best predictor. An increase in moderate PA was associated with a decrease in SoU. Additional predictors of the effects of PA on SoU were identified; moderate intensity PA was associated with SoU after controlling for MPSS and an alcohol consumption (participants were classified as “not drinking alcohol”, “light/moderate drinkers”, and “heavy drinkers”). An increase in MPSS was associated with an increase in SoU, while increase in alcohol consumption was associated with a decrease of SoU. In addition, alcohol consumption was found to be a moderator of the relationship; for “heavy drinkers” increased minutes of moderate PA appeared to be associated with increased cravings. However, results of this study exploratory must be interpreted with caution. Further research into the moderating effects of alcohol drinking on the effects of habitual PA on cigarette cravings is needed. The results of this chapter are being prepared for a submission in the Psychopharmacology journal.

Appendices

Appendix A; Chapter 1: Introduction

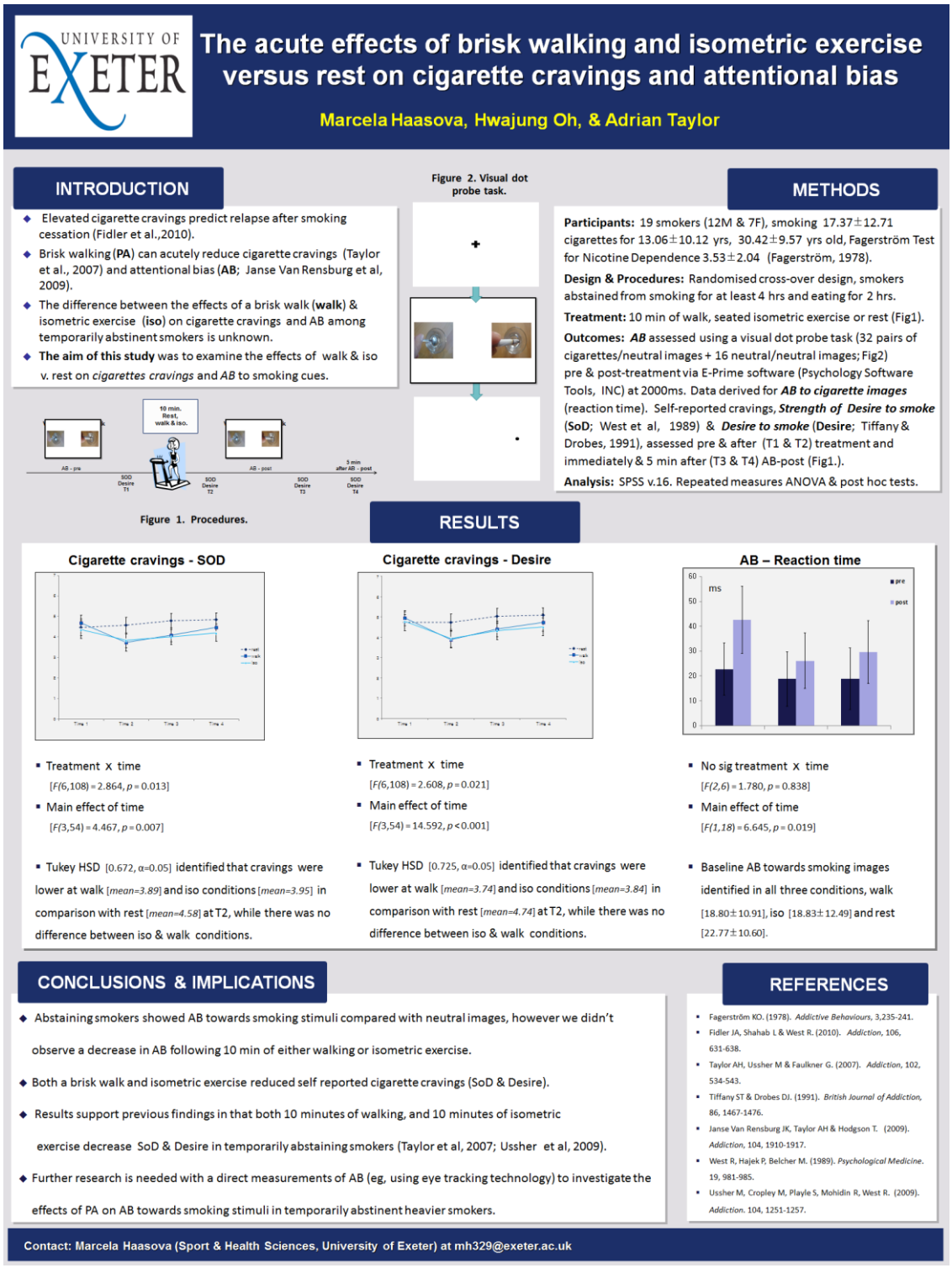


Figure 23 Poster presented at ASH Wales, 2011

Haasova M, Warren FC, Ussher M, Janse Van Rensburg K, Faulkner G, Cropley M, Byron-Daniel J, Everson-Hock ES, Oh H, Taylor AH (2013) The acute effects of physical activity on cigarette cravings: systematic review and meta-analysis with individual participant data. Addiction 108 (1): 26-37.

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 shorts 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 standardized mean difference (SMD) between PA and control conditions (across 15 primary studies) of -1.91 [95% confidence interval (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.

The full publication is available at:
http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.2012.04034.x/abstract

Haasova M, Warren FC, Ussher M, Janse Van Rensburg K, Faulkner G, Cropley M, Byron-Daniel J, Everson-Hock ES, Oh H, Taylor AH (2014) The acute effects of physical activity on cigarette cravings: Exploration of potential moderators, mediators and physical activity attributes using individual participant data (IPD) meta-analyses. Psychopharmacology 231(7):1267-75.

Abstract:

RATIONALE:
The effects of acute bouts of physical activity (PA) on Strength of Desire (SoD) and Desire to Smoke (DtS) using individual participant data (IPD) from 19 acute randomised controlled studies were quantified. However, there is a need to identify factors influencing this relationship.
OBJECTIVES:
To understand who most benefits from PA, whether changes in affect mediate these effects and whether any specific attributes of PA are associated with cigarette cravings.
METHODS:
IPD (n = 930) contributed to one-stage IPD meta-analyses. Participants engaging in PA were compared against controls, using post-intervention DtS and SoD (when DtS is not available) with baseline adjustments. The craving scales were linearly rescaled to 0-100 % (a mean difference between groups of -10 would indicate that post-intervention cravings were 10 % lower in the PA compared with the control group). Demographic, smoking and other characteristics were examined as predictors and potential moderators, whereas change in affect was considered as a mediator. PA was categorised according to type, duration and intensity, to determine PA attributes associated with cravings reduction.
RESULTS:
None of the included covariates were shown to moderate or mediate the effects of PA. Intensity of PA was significantly associated with a reduction in cravings; moderate and vigorous intensity PA offered the most benefits. A one-stage IPD meta-analysis yielded effect sizes of -9.22 (-15.24; -3.20) for light, -34.57 (-42.64; -26.50) for moderate and -31.29 (-38.00; -24.57) for vigorous intensity in comparison with controls.
CONCLUSIONS:
Moderate intensity PA could be recommended to all smokers regardless of demographic, smoking and other characteristics.

The full publication is available at:
http://link.springer.com/article/10.1007%2Fs00213-014-3450-4

UNIVERSITY OF EXETER

The acute effects of physical activity on cigarette cravings: A meta-analysis with individual participant data (IPD).

Haasova, M.[1], Janse Van Rensburg, K.[2], Faulkner, G.[3], Ussher, MH.[4], Warren, F.[5], Taylor, A.H.[1]

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Introduction

- Elevated cigarette cravings predict relapse after smoking cessation[1].
- Small scale studies suggest that, during temporary abstinence, a single session of physical activity (PA) acutely reduces Strength of Desire (SoD)[2] to smoke[3], but there has been no review since 2006[3] and no meta-analyses. Also, there has been no attempt to identify what factors influence this effect.
- Individual participant data (IPD) analysis involves the pooling of raw data from small studies, and can then allow detection of variables that moderate any effects[4,5].

Aims

Following a systematic review[3], this study aims to employ IPD to quantify the effects of PA on cravings and to identify predictors of craving reduction.

Methods

- Sixteen randomised parallel group or crossover design studies met the inclusion criteria. Original data from the authors were collated and all analyses used Stata v.11.
- A two-stage IPD meta-analysis was performed using data from 8 parallel arm trials and randomly selected data from 7 crossover trials, using a random effects model. Participants engaging in PA were compared against controls, using the difference between post-intervention and baseline SoD.
- Linear regression of post-PA SoD with demographic & behavioural covariates followed, adjusting for study and baseline SoD.

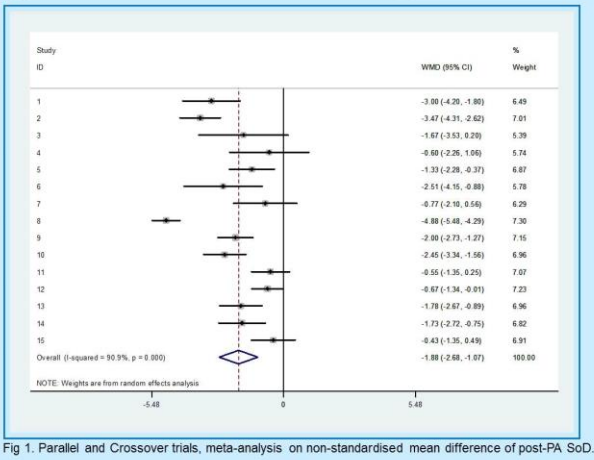

Fig 1. Parallel and Crossover trials, meta-analysis on non-standardised mean difference of post-PA SoD.

Results

As expected there was a greater reduction in SoD following exercise compared to control.
For the two-stage meta-analysis, the pooled estimate for treatment effect (non-standardised mean difference) was:

-1.877 (95% CI -2.679; -1.074)

with a high degree of between-study heterogeneity.

- IPD with SoD & covariates were available in 14 trials (n= 864). Age, smoking years (SY), cigarettes per day (CPD) and carbon monoxide (CO) were significant individually ($p<0.05$). CO and SY data were only available from 8 & 9 studies respectively. Age was highly correlated with SY (r=0.924) and used as a proxy.
- A model including age and CPD was considered the most appropriate. The regression coefficients for age and CPD were:

-0.031 (95% CI -0.052; -0.010; p=0.004) and 0.034 (95% CI 0.004; 0.064; p=0.026) respectively.

- Gender, body mass index, PA status, Fagerström Test for Nicotine Dependence[6] and duration of abstinence, were not individually associated with post-PA SoD.

Summary

- This is the first quantitative synthesis of the acute effects of PA on cigarette cravings. We found a large positive effect of a single session of PA on cigarette cravings (despite a high level of between study heterogeneity).
- Data from 350 smokers suggest that those who were older and smoked more cigarettes had a greater benefit of exercise.
- A single session of PA can be a powerful aid to help temporarily abstinent smokers to resist cigarettes cravings.
- Future work is planned in this area to identify the optimal dose to maximise the effects of exercise.

References:
(1) Fidler JA, Shahab L, West R. (2010). Addict, 106, 631-8. (2) West R, Hajek P, Belcher M (1989) Psychol Med, 19, 981-985. (3) Taylor, AH, Ussher, MH, Faulkner, G. (2007). Addict, 102, 534-543. (4) Parmar MK, Stewart, LA, & Altman, DG (1996). Br J Cancer, 74(4), 496-501. (5) Riley RD, Lambert PC & Abo-Zaid G. (2010). BMJ, 340:c221. (6) Heatherton TF, Kozlowski LT, Fagerström KO(1991). Br J Addict, 86, 1119-27.

Figure 24. Poster presented at ECSS Liverpool, 2

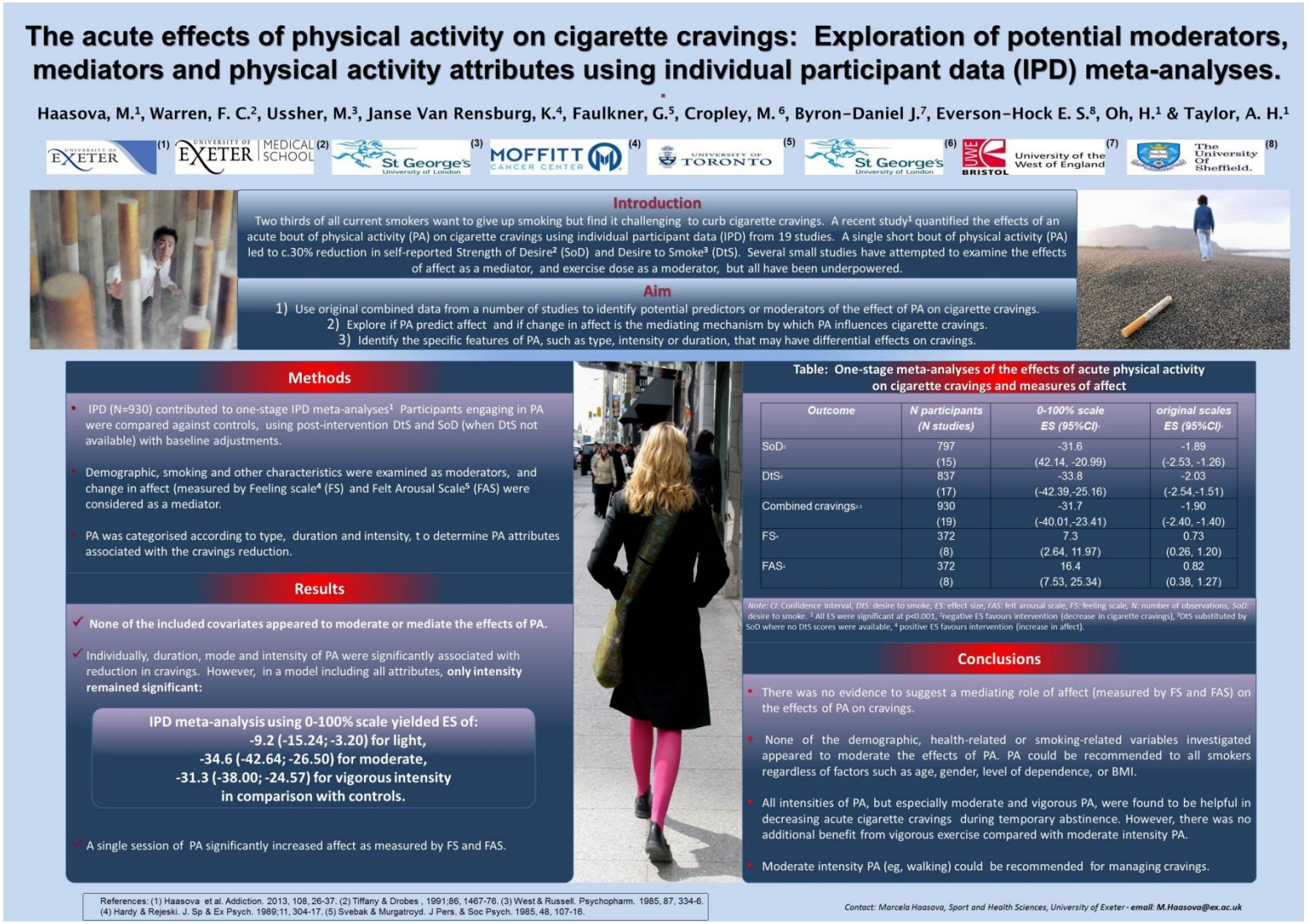

Figure 25. Poster presented at SRNT Boston, 2013

Appendix B; Chapter 2: Literature review

Table 34. The Minnesota Withdrawal Scale, considered symptoms

DSM-III
Cravings for tobacco
Irritability
Anxiety
Difficulty concentrating
Restlessness
Headaches
Drowsiness
Gastrointestinal tract problems
Other
Fatigue
Impatience
Somatic complaints (e.g. sweating, dizziness)
Sleep (decrease in adequacy, increase in latency, number of awakening, time awake, and decrease in time asleep)
Eating and drinking (hunger, alcohol intake increase, caffeine intake decrease)

Table 35. An online version of Minnesota Withdrawal Scale, Self-Report

Behavior Rating Scale Self-Report Please rate yourself for the period for the last _____ 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe
1. Angry, irritable, frustrated
2. Anxious, nervous
3. Depressed mood, sad
4. Desire or craving to smoke
5. Difficulty concentrating
6. Increased appetite, hungry, weight gain
7. Insomnia, sleep problems, awakening at night
8. Restless
9. Impatient
10. Constipation
11. Dizziness
12. Coughing
13. Dreaming or nightmares
14. Nausea
15. Sore throat

Table 36. An online version of Minnesota Withdrawal Scale, Observer rating

Behavioral Rating Scale Observer Rating Rate the subject on the following symptoms according to whether you observed the symptom in the subject in the last _____. It does not matter whether the subject complained of the symptom. We want to know whether you noticed the symptom. 0 = not at all, 1 = slight, 2 = mild, 3 = moderate, 4 = severe
a. Angry/irritable/frustrated
b. Anxious/tense
c. Depressed
d. Restless/Impatient
How confident are you that this rating is accurate?
0 = not at all
1 = somewhat confident
2 = moderately confident
3 = very confident

Table 37. The Wisconsin Smoking Withdrawal Scale

0 = Strongly disagree 1 = Disagree 2 = Feel neutral 3 = Agree 4 = Strongly agree	
1. Food is not particularly appealing to me.	Hunger *
2. I am getting restful sleep.	Sleep*
3. I have been tense or anxious.	Anxiety
4. My level of concentration is excellent.	Concentration *
5. I awaken from sleep frequently during the night.	Sleep
6. I have felt impatient.	Anxiety
7. I have felt upbeat and optimistic.	Sadness*
8. I have found myself worrying about my problems	Anxiety
9. I have had frequent urges to smoke.	Cravings
10. I have felt calm lately.	Anxiety *
11. I have been bothered by the desire to smoke a cigarette.	Cravings
12. I have felt sad or depressed.	Sadness
13. I have been irritable, easily angered.	Anger
14. I want to nibble on snacks or sweets.	Hunger
15. I have been bothered by negative moods such as anger, frustration, and irritability.	Anger
16. I have been eating a lot.	Hunger
17. I am satisfied with my sleep.	Sleep*
18. I have felt frustrated.	Anger
19. I have felt hopeless or discouraged.	Sadness
20. I have thought about smoking a lot.	Cravings
21. I have felt hungry.	Hunger
22. I feel that I am getting enough sleep.	Sleep*
23. It's hard to pay attention to things.	Concentration
24. I have felt happy and content.	Sadness*
25. My sleep has been troubled.	Sleep
26. I have trouble getting cigarettes off my mind.	Cravings
27. It had been difficult to think clearly.	Concentration
28. I think about food a lot.	Hunger
16. I have been eating a lot.	Hunger
17. I am satisfied with my sleep.	Sleep*
18. I have felt frustrated.	Anger
19. I have felt hopeless or discouraged.	Sadness
20. I have thought about smoking a lot.	Cravings
21. I have felt hungry.	Hunger

22. I feel that I am getting enough sleep.	Sleep*
23. It’s hard to pay attention to things.	Concentration
24. I have felt happy and content.	Sadness*
25. My sleep has been troubled.	Sleep
26. I have trouble getting cigarettes off my mind.	Cravings
27. It had been difficult to think clearly.	Concentration
28. I think about food a lot.	Hunger

Notes: * items are reversed scored

Table 38. QSU-brief; 10-item questionnaire

1	I have a desire for a cigarette right now.
2	Nothing would be better than smoking a cigarette right now.
3	If it were possible, I probably would smoke now.
4	I could control things better right now if I could smoke
5	All I want right now is a cigarette.
6	I have an urge for a cigarette.
7	A cigarette would taste good now.
8	I would do almost anything for a cigarette now.
9	Smoking would make me less depressed.
10	I am going to smoke as soon as possible

Note: questionnaire assesses cigarette cravings using a 100–point scale ranging from strongly disagree to strongly agree.

Table 39. Toll and colleagues 12−item, two factors questionnaire

Intention/desire to smoke factor:	
1	Smoking a cigarette would not be pleasant.
2	Even if it were possible, I probably wouldn't smoke now.
3	I have no desire for a cigarette right now
4	A cigarette would not taste good right now
5	I have an urge for a cigarette
6	I am going to smoke as soon as possible.
Negative affect or withdrawal factor:	
1	Nothing would be better than smoking a cigarette right now
2	Smoking would make me less depressed
3	All I want right now is a cigarette
4	Smoking now would make things seem just perfect.
5	I could control things better right now if I could smoke
6	I would do almost anything for a cigarette now

Table 40. The Tobacco Craving Questionnaire-Short form

Emotionality
I would be less irritable now if I could smoke.
If I were smoking now I could think more clearly.
I could control things better right now if I could smoke.
Expectancy
I would enjoy a cigarette right now.
A cigarette would taste good right now.
Smoking a cigarette would be pleasant.
Compulsivity
If I smoked right now, I would not be able to stop.
I could not stop myself from smoking if I had some cigarettes here.
I would not be able to control how much I smoked if I had some cigarettes here.
Purposefulness
If I had a lit cigarette in my hand, I probably would smoke it.
It would be hard to pass up the chance to smoke.
I could not easily limit how much I smoked right now.

Table 41. The Cigarette Withdrawal Scale, a 21-item six-dimension scale

Depression–anxiety
I feel depressed
My morale is low
I feel worried
I feel anxious
Cravings
The only thing I can think about is smoking a cigarette
I miss cigarettes terribly
I feel an irresistible need to smoke
I would like to hold a cigarette between my fingers
Irritability–impatience
I am irritable
I get angry easily
I have no patience
I feel nervous
Difficulty concentrating
I find it difficult to think clearly
I find it hard to concentrate
I find it hard to focus on the task at hand
Appetite–weight gain
I am eating more than usual
My appetite has increased
I have put on weight recently
Insomnia
I have difficulty sleeping
I wake up often during the night
I have trouble falling asleep at night

Appendix C; Chapter 3: Research design

Study 1: The effects of brisk walking and seated isometric exercise on cigarette cravings and attentional bias to smoking cues

Table 42. Study 1; self-reported questionnaires

Outcome	Outcome description	
Cravings	Strength of Desire to Smoke (West and Hajek 2004; West et al. 1989; West and Russell 1985) *'How strong is your desire to smoke right now?'*	Self-reported; 1−7 point response scales: 1: very weak, 4: neither strong or weak, 7: very strong.
	Desire to Smoke (Tiffany and Drobes 1991) *'I have a desire for a cigarette right now.'*	Self-reported; 1−7 point response scales. 1: strongly disagree, 4: neither agree or disagree, 7: strongly agree.
Withdrawal Symptoms	MPSS (West and Hajek 2004): Irritable Restless, Depressed, Hungry, Poor concentration, Anxious, Poor sleep at night	Self-reported; 0−4 point response scale. 0: not at all, 1: slightly, 2: somewhat, 3: very, 4: extremely.
Affect measures	Feeling Scale (Hardy and Rejeski 1989)	Self-reported; -5− +5 point response scale. +5:very good,+3:good,+1: fairly good,0:neutral, -1:fairly bad, -3 bad, -5:very bad.
	Felt Arousal Scale (Svebak and Murgatroyd 1985)	Self-reported; 1−6 point response scales. 1: Low arousal, 6: high arousal.
Physical activity	Seven Day Recall Physical Activity Questionnaire (Blair et al. 1985)	Self-reported minutes of vigorous and moderate intensity PA in the past week. In addition, average time of sleep per day is recorded. It is assumed that time not recorded as spent, vigorous PA and moderate PA is spent in light intensity PA.

Notes: MPSS = Mood and Physical Symptoms Scale; PA = physical activity.

Study 2: The acute effects of physical activity on cigarette cravings: Systematic review and individual participant data meta-analysis

Table 43. Study 2; self-reported questionnaires and extracted data

Outcome	Outcome description	
Cravings	Strength of Desire to Smoke (West and Hajek 2004; West et al. 1989; West and Russell 1985) *"How strong is your desire to smoke right now?"*	Self-reported; 1−7 point response scales. 1: very weak, 4: neither strong or weak, 7: very strong.
	Desire to Smoke (Tiffany and Drobes 1991) *"I have a desire for a cigarette right now."*	Self-reported; 1−7 point response scales. 1: strongly disagree, 4: neither agree nor disagree, 7: strongly agree.
PA	Information about intensity of PA, duration of PA, and type of PA was extracted.	
Age	In years	
Type of PA	Isometric, cycling, isometric exercise.	
Published study	Published/unpublished study.	

Notes: PA = physical activity.

Study 3: The acute effects of physical activity on cigarette cravings: Exploration of potential moderators, mediators and physical activity attributes using systematic review and individual participant data meta-analyses

Table 44. Study 3; self-reported questionnaires and extracted data

Outcome	Outcome description	
Cravings	Strength of Desire to Smoke (West and Hajek 2004; West et al. 1989; West and Russell 1985) *"How strong is your desire to smoke right now?"*	Self-reported; 1−7 point response scales. 1: very weak, 4: neither strong or weak, 7: very strong.
	Desire to Smoke (Tiffany and Drobes 1991) *"I have a desire for a cigarette right now."*	Self-reported; 1−7 point response scales. 1: strongly disagree, 4: neither agree or disagree, 7: strongly agree.
Affect measures	Feeling Scale (Hardy and Rejeski 1989)	Self-reported; -5− +5 point response scale. +5:very good,+3:good,+1: fairly good,0:neutral, -1:fairly bad, -3 bad, -5:very bad.
	Felt Arousal Scale (Svebak and Murgatroyd 1985)	Self-reported; 1−6 point response scales. 1: low arousal, 6: high arousal.
Cigarette dependence	(FTCD; Fagerström 1978; 2012)	Self-reported; six questions, score of 1–2 indicates low dependence, 3–4 low to moderate dependence , 5–7 moderate dependence and 8–10 high dependence.
PA	Information about intensity of PA, duration of PA, and type of PA was extracted.	
Age	In years.	
Gender	Males and females.	
BMI	Weight (kg)/ height ^{2}(m).	
Resting HR	Beats per minutes.	
Smoking measures	Number of years the participant had been smoking, carbon monoxide measures taken prior to the start of the intervention, duration of abstinence period.	

Notes: FTCD = Fagerström Test of Cigarette Dependence; BMI = Body Mass Index (kg/m2); MPSS = Mood and Physical Symptoms Scale.

Study 4: How habitual physical activity and other individual characteristics influence cigarette cravings, an exploration of baseline measures from the Exercise Assisted Reduction then Stop (EARS) smoking study.

Table 45. Study 4; Outcomes assessed at baseline

Outcome	Outcome description		
Cravings	Cravings	*The Strength of Urge to smoke (SoU; West and Hajek 2004; West and Russell 1985): "How strong have the urges been to smoke this past week?".* *Time Spent with Urges in the past week (TSwU; West and Hajek 2004): "How much of the time have you felt the urge to smoke in the past week?".*	Self-reported; 1−6 point response scales
Withdrawal and mood	Withdrawal Symptoms	*MPSS (West and Hajek 2004):*	Self-reported; 1−5 point response scale
	Quality of Life	*EQ-5D-3L(Prieto and Sacristan 2004).*	Self-reported
	Subjective Stress	*PSS (Cohen et al. 1983)*	Self-reported, 4 items
Physical Activity	Habitual levels of PA	*7 Day PA Recall (Blair et al. 1985).*	Self-reported: (1) Light, moderate, and vigorous PA; minutes per day (2) Energy expenditure; kcal/kg
	Cognitive	Confidence for undertaking PA	Self-reported; 1−7 point response scale: How *confident* are you to: (1) Do at least 30 minutes of moderate intensity PA on most days of the week, over

			the next 6 months? (2) Walk continuously for 15 minutes at a brisk pace?
		SOC to use PA to control smoking (Pre-contemplation, contemplation, planning, action, and maintenance stage)	Self-reported: choose one from the following five options: (1) I do not use PA as a way of controlling my cigarette smoking *and I don't intend to start. (2)* I do not use PA as a way of controlling my cigarettes smoking *but I'm thinking of starting. (3)* I use PA once in a while as a way of controlling my cigarette smoking, but not regularly. (4) I use PA regularly as a way of controlling my cigarette smoking, but only started within the past six months. (5) I use PA regularly as a way of controlling my cigarette smoking and have been doing so for longer than six months.
Smoking	Behavioural	*Self-reported cigarettes*	number of cigarettes smoked per day
		Self-reported smoking history	*Age when participants started smoking*, number of quit attempts and attempts at cutting down in the past year, the longest period of cessation in the past year, cessation aids used in the past year, and the use of SSS in the past.
	Nicotine Dependence	*FTCD* (Fagerström 1978; 2012)	Self-reported; six questions, score of 1–2 indicates low dependence, 3–4 low to moderate dependence , 5–7 moderate dependence and 8–10 high dependence.
	Smoking Satisfaction	*mCEQ (Cappelleri et al. 2007)*	Self-reported; reward and satisfaction.
	Cognitive	Confidence and Importance of quitting	Self-reported; 1−7 point response scale: (1) How important is it for you to stop smoking permanently and completely in the next six months? (2) How confident are you that you can stop smoking permanently and completely in the next six months? (3) An important person in your life thinks you should

			quit smoking. And (4) How confident are you that in 4 weeks you will smoke only half the amount of cigarettes you smoke now?
Alcohol consumption	Behavioural	*Adapted AUDIT questionnaire (Allen et al. 1997)*	Self-reported; 1−5 point response scales: (1) How often do you have a drink containing alcohol? (2) How many drinks containing alcohol do you have on a typical day when you are drinking? And 1−6 point response scale: (3) How many drinks containing alcohol have you had in the past week?
Demographics	Self-reported; age (continuous data), *gender* (binary data), cohabiting status (binary data), cohabiting with other smokers (binary data), parental status (binary data), *employment* (employed/unemployed, binary data), age of leaving full time education (continuous data), ethnicity (binary data), BMI (kg/m^2, continuous data).		

Notes: outcomes highlighted in italic were considered in Study 4; AUDIT = The Alcohol Use Disorders Identification Test; BMI = Body Mass Index, CO = carbon monoxide; EQ-5D-3L = three level European Quality of Life-5 Dimension questionnaire; mCEQ = modified Cigarette Evaluation Questionnaire; MPSS = Mood and Physical Symptoms Scale; EARS = The Exercise Assisted Reduction then Stop; FTCD = Fagerström Test for Cigarette Dependence; PA = physical activity; PSS = Perceived Stress Scale; SOC = Stages of readiness to change; SSS = Stop Smoking Services.

Appendix D; Chapter 4: The effects of brisk walking and seated isometric exercise on cigarette cravings and attentional bias to smoking cues

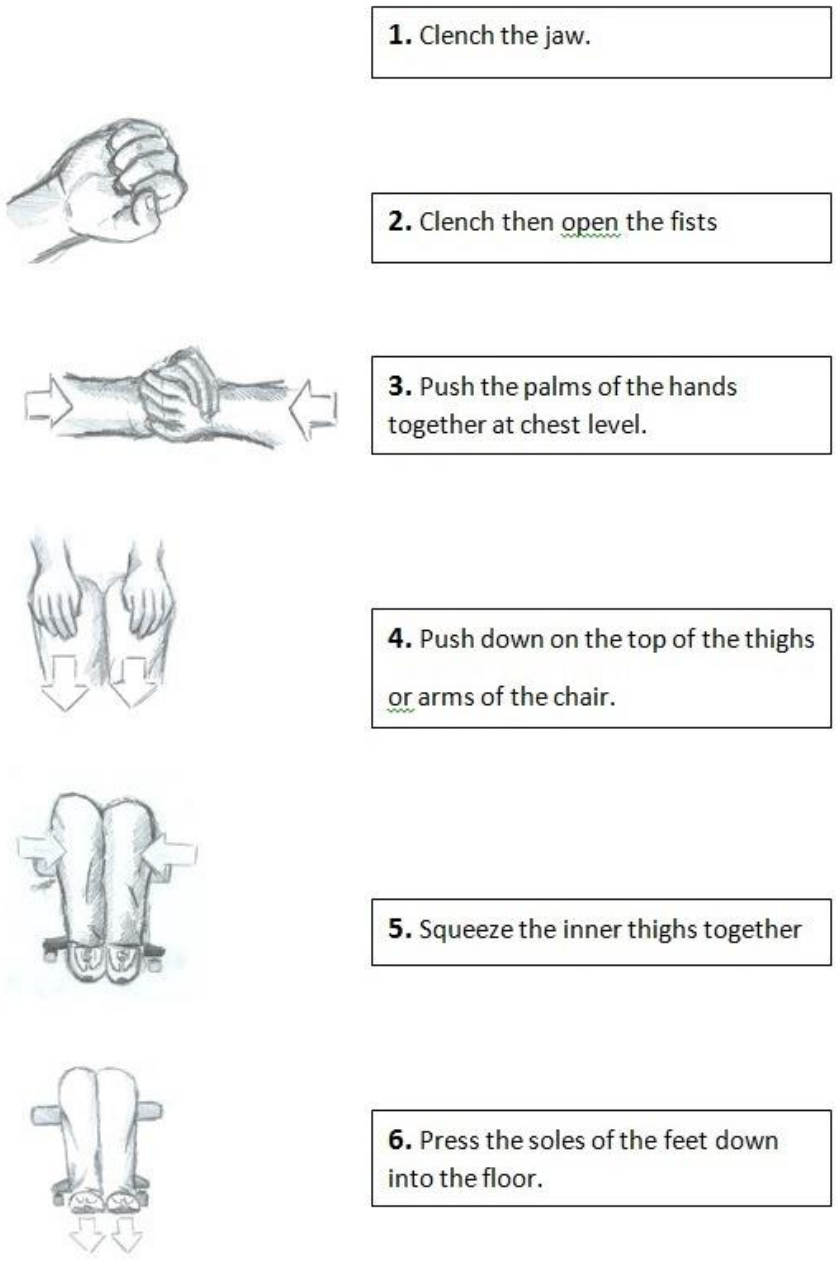

Figure 26. Isometric exercises used in Study 1 (Chapter 4)

Table 46 Strength of Desire; results of a linear mixed model using only baseline and post treatment cravings values

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	0.35 (-0.29; 0.99)	1.07 (0.285)
	ISO	-0.10 (-0.74; 0.54)	-0.31 (0.760)
Time	T1	0.25 (-0.39; 0.89)	0.76 (0.445)
Treatment/ time interaction	Walk/T1 interaction	-1.25 (-2.11; -0.29)	-2.59 (0.009)
	ISO/T1 interaction	-0.75 (-1.66; 0.16)	-1.62 (0.105)
Wald chi^2 statistic		Chi^2 = 15.57, df = 5, p = 0.008	
Global Wald chi^2 statistic treatment		Chi^2 = 4.22, df = 2, p = 0.121	
Global Wald chi^2 statistic of the time		Chi^2 = 4.49, df = 1, p = 0.034	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 6.87, df = 2, p = 0.032	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” was the baseline category for time; 95 % CI = 95% Confidence Interval; T1= post intervention; ISO = isometric exercise condition; Walk= w alking condition.

Table 47 Strength of Desire; results of a linear mixed model using the combine physical activity condition

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	PA condition	0.13 (-0.39; 0.64)	0.47 (0.637)
Time	T1	0.25 (-0.35; 0.85)	0.82 (0.414)
	T2	0.45 (-0.15; 1.05)	1.47 (0.141)
	T3	0.45 (-0.15; 1.05)	1.47 (0.141)
Treatment/ time interaction	PA condition /T1 interaction	-0.98 (-1.71; -0.24)	-2.60 (0.009
	PA condition /T2 interaction	-0.88 (-1.61; -0.14)	-2.34 (0.019)
	PA condition /T3 interaction	-0.58 (-1.31; 0.16)	-1.54 (0.125)
Wald chi^2 statistic		Chi^2 = 29.64, df = 7, p < 0.001	
Global Wald chi^2 statistic treatment		Chi^2 = 13.21, df = 1, p < 0.001	
Global Wald chi^2 statistic of the time		Chi^2 = 4.68, df = 3, p = 0.197	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 8.235, df = 3, p = 0.042	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2.

Table 48 Desire to Smoke; results of a linear mixed model using only baseline and post treatment cravings values

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	0.20 (-0.37; 0.77)	0.68(0.494)
	ISO	0.05 (-0.52; 0.62)	0.17 (0.864)
Time	T1	0.00 (-0.57; 0.57)	-0.00 (1.000)
Treatment/ time interaction	Walk/T1 interaction	-0.95 (-1.50; -0.00)	-2.30 (0.022)
	ISO/T1 interaction	-0.70 (-1.35; 0.14)	-1.69 (0.091)
Wald chi^2 statistic		Chi^2 = 18.85, df = 5, p = 0.002	
Global Wald chi^2 statistic treatment		Chi^2 = 2.59, df = 2, p = 0.274	
Global Wald chi^2 statistic of the time		Chi^2 = 10.60, df = 1, p = 0.001	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 5.66, df = 2, p = 0.059	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; ISO = isometric exercise condition; Walk = walking condition.

Table 49 Desire to Smoke; results of a linear mixed model using the combined physical activity condition

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	PA condition	0.13 (-0.33; 0.58)	0.54 (0.589)
Time	T1	0.00 (-0.52; 0.52)	0.00 (1.000)
	T2	0.30 (-0.22; 0.82)	1.12 (0.262)
	T3	0.40 (-0.12; 0.92)	1.50 (0.134)
Treatment/ time interaction	PA condition /T1 interaction	-0.83 (-1.47; -0.18)	-2.52 (0.012)
	PA condition /T2 interaction	-0.78 (-1.42; -0.13)	-2.37 (0.018)
	PA condition /T3 interaction	-0.60 (-1.24; 0.0.4)	-1.83 (0.067)
Wald chi^2 statistic		Chi^2 = 38.55, df = 7, p < 0.001	
Global Wald chi^2 statistic treatment		Chi^2 = 13.49, df = 1, p < 0.001	
Global Wald chi^2 statistic of the time		Chi^2 = 11.04, df = 3, p = 0.012	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 8.05, df = 3, p = 0.045	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" was the baseline category for time; 95 % CI= 95% Confidence Interval; T1= post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2; PA condition = physical activity condition.

Table 50 Mood and physical symptoms scale; results of a linear mixed model using only baseline and post treatment cravings values

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	Walk	-0.11 (-0.37; 0.15)	-0.84 (0.400)
	ISO	-0.14 (-0.40; 0.12)	-1.07 (0.285)
Time	T1	0.15 (-0.11; 0.41)	1.15 (0.252)
Treatment/ time interaction	Walk/T1 interaction	-0.27 (-0.63; 0.10)	-1.43 (0.152)
	ISO/T1 interaction	-0.46 (-0.82; 0.10)	-2.49 (0.013)
Wald chi^2 statistic		Chi^2 = 24.22 df = 5, p < 0.001	
Global Wald chi^2 statistic treatment		Chi^2 = 16.51, df = 2, p < 0.001	
Global Wald chi^2 statistic of the time		Chi^2 = 1.47, df = 1, p = 0.225	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 6.23, df = 2, p = 0.044	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” was the baseline category for time; 95 % CI = 95% Confidence Interval; T1= post intervention; ISO = isometric exercise condition; Walk = walking condition.

Table 51 Mood and physical symptoms scale; results of a linear mixed model using the combined physical activity condition

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	PA condition	-0.13 (-0.34; 0.09)	-1.16 (0.244)
Time	T1	0.15 (-0.09; 0.39)	1.21 (0.226)
	T2	0.29 (-0.05; 0.53)	2.34 (0.019)
	T3	0.25 (-0.01; 0.49)	2.02 (0.044)
Treatment/ time interaction	PA condition /T1 interaction	-0.36 (-0.66; -0.07)	-2.39 (0.017)
	PA condition /T2 interaction	-0.28 (-0.58; 0.017)	-1.84 (0.065)
	PA condition /T3 interaction	-0.27 (-0.58; 0.027)	-1.78 (0.075)
Wald chi^2 statistic		Chi^2 = 58.50, df = 7, p < 0.001	
Global Wald chi^2 statistic treatment		Chi^2 = 43.31, df = 1, p < 0.001	
Global Wald chi^2 statistic of the time		Chi^2 = 8.00, df = 3, p = 0.046	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 6.47, df = 3, p = 0.091	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; T2 = post the second probe task; T3 = 5 minutes after time T2; PA condition = physical activity condition.

Table 52 Percentage dwell time; results of a linear mixed model using the combined physical activity condition

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	PA condition	-0.43 (-3.24; 2.38)	-0.30 (0.766)
Time	T1	0.84 (-2.40; 4.09)	0.51 (0.611)
Treatment/ time interaction	PA condition /T1 interaction	-1.29 (-5.26; 2.69)	-0.63 (0.526)
Wald chi^2 statistic		Chi^2 = 1.52 df = 3, p = 0.678	
Global Wald chi^2 statistic treatment		Chi^2 = 1.11, df = 1, p = 0.291	
Global Wald chi^2 statistic of the time		Chi^2 = 0.04, df = 1, p = 0.845	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 0.40, df = 1, p = 0.526	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; PA condition = physical activity condition.

Table 53 Percentage first fixation; results of a linear mixed model using the combined physical activity condition

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	PA condition	-3.92 (-8.48; 0.66)	-1.68 (0.0.93)
Time	T1	-4.51 (-9.78; 0.77)	-1.67 (0.0.94)
Treatment/ time interaction	PA condition /T1 interaction	2.58 (-3.88; 9.04)	0.78 (0.434)
Wald chi^2 statistic		Chi^2 = 6.36, df = 3, p = 0.096	
Global Wald chi^2 statistic treatment		Chi^2 = 2.53, df = 1, p = 0.111	
Global Wald chi^2 statistic of the time		Chi^2 = 3.80, df = 1, p = 0.051	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 0.61, df = 1, p = 0.434	

Notes: “Control rest condition” was the baseline category for treatment; “baseline time” was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; PA condition = physical activity condition.

Table 54 Reaction Time Attentional Bias Score; results of a linear mixed model using the combined physical activity condition

Variable		Mean difference (95% CI)	z-test (p-value)
Treatment	PA condition	-0.38 (-22.47; 21.70)	-0.03 (0.937)
Time	T1	25.96 (0.46; 51.46)	2.00 (0.046)
Treatment/ time interaction	PA condition /T1 interaction	-18.05 (-49.28; 13.19)	-1.13 (0.257)
Wald chi^2 statistic		Chi^2 = 6.11 df = 3, p = 0.106	
Global Wald chi^2 statistic treatment		Chi^2 = 1.39, df = 1, p = 0.238	
Global Wald chi^2 statistic of the time		Chi^2 = 4.52, df = 1, p = 0.034	
Global Wald chi^2 statistic of the treatment/time interaction		Chi^2 = 1.28, df = 1, p = 0.258	

Notes: "Control rest condition" was the baseline category for treatment; "baseline time" was the baseline category for time; 95 % CI = 95% Confidence Interval; T1 = post intervention; PA condition = physical activity condition.

Table 55 Power size calculation for future studies investigating the effects of PA on attentional bias

		Maintenance AB		Initial AB	
Power	**Difference***	**Mean (SD)[a]**	**Sample size**	**Mean (SD)[a]**	**Sample size**
80%	**10%**	51.2 (9.1) 56.2 (9.1)	N1 = 52 N2 = 52	48.8 (6.1) 53.8 (8.5)	N1 = 35 N2 = 35
90%	**10%**	51.2 (9.1) 56.2 (9.1)	N1 = 70 N2 = 70	48.8 (6.1) 53.8 (8.5)	N1 = 47 N2 = 47
80%	**15%**	51.2 (9.1) 56.2 (9.1)	N1 = 21 N2 = 21	48.8 (6.1) 53.8 (8.5)	N1 = 18 N2 = 18
90%	**15%**	51.2 (9.1) 56.2 (9.1)	N1 = 28 N2 = 28	48.8 (6.1) 53.8 (8.5)	N1 = 24 N2 = 24

Notes: Calculations are based on a parallel arms design with two conditions (i.e. control and PA conditions), and two treatment measurements (i.e. pre and post treatment measurement; the correlation between pre and post treatment measures was assumed to be 0); * = to detect approximately 10% and 15% change in the outcomes; a = the mean and SD refer to the mean and SD post treatment in the current study (T1) in the walking and the control group respectively; AB = Attentional Bias, N1 = needed sample size for an PA intervention group; N2 = needed sample size for a control group; SD = standard deviation.

Appendix E; Chapter 5: The acute effects of physical activity on cigarette cravings: Systematic review and individual participant data meta-analysis

Table 56. Summary of studies included in quantitative synthesis

Study (in chronological order)	Design & cravings measures	Interventions	Subjects	Reported cravings related findings
Ussher and colleagues (2001) Abstinence: required = 15 hrs.	Parallel arm design. Measures pre (T1), mid (T2), immediately post (T3), 5 min (T4) & 10 min post treatment (T5). BaselineSoD = 6.3. Baseline DtS = 6.4.	All 10 min & 1-2 min warm up. (a) video + cycling @ 40-60% HRR, N = 42. (b) video control, N = 18. (c) passive control, N = 18.	Inactive 78 M & F. Mean age = 36.2 yrs. Mean FTCD = 5.9. Mean CPD = 18.0. Mean SY = 18.5 yrs.	(a) < (b & c) for SoD & DtS at T1-T5. When compared to baseline SoD & DtS: (a) < (b & c) for SoD & DtS at T1-T5. No difference between (b) & (c). Effects greater for less active. *Both (b) & (c) as control conditions in the MA*.
Daniel and colleagues (2004) Abstinence: mean = 13.3hrs.	Parallel arm design. Measures pre (T1), mid (T2), post (T3), 5 min (T4) & 10 min post treatment (T5). BaselineSoD = 3.8*. Baseline DtS = 3.8*.	All 5 min cycling and 2.5 min warm-up & cool-down. (a) cycling @ 40-60% HRR. (b) cycling @ 10-20% HRR. (c) passive control.	Inactive 84 M & F, N = 28 in each group. Mean age = 30.1 yrs. Mean FTCD = 4.0. Mean CPD = 16.8. Mean SY = 12.6 yrs.	Results reported as SoD & DtS change scores from baseline. (a) > (b & c) decrease change scores for DtS (T2 & T3) and SoD (T2-T4) & (a) > (b) decrease in SoD change scores (T5). *Both (b) & (c) as control conditions in the MA*.
Taylor and colleagues (2005)	Cross-over design. Measures pre (T1), mid	Up to 40 min. (a) self-paced 1 mile brisk	Active, 10M & 5F. Mean age = 25.6yrs	(a) < (b) SoD at T2-T5 and both QSU scales at T5.

Abstinence: required = 15 hrs.	(T2), immediately post (T3), 10 min. (T4) & 20 min post treatment (T5). BaselineSoD = 5.7. Baseline DtS = 6.1*. *Only SoD reported in the article, DtS was a part of QSU.*	walk @ mean RPE = 10.8, mean RPE % HRR = 24.5 & 2 min warm up & cool down, mean time =18 min. (b) passive control, time = 40 min.	Mean FTCD = 4.0	
Daniel and colleagues (2006) Abstinence: mean = 13.6 hrs.	Parallel arm design. Measures pre (T1: mean of 10, 5 & 0 min pre), during (T2: mean of mid and end) & post treatment (T3: mean of 5 & 10 min post). BaselineSoD = 4.2*. Baseline DtS = 4.5*.	All 10 min. (a) cycling @ 40-60% HRR & 1-2 min warm up. (b) passive control (cognitive distraction task).	Sedentary, 23 M & 17 F. Mean age = 23.4 yrs. Mean CPD = 14.0. Mean FTCD = 3.1. Mean SY = 6.4 yrs.	(a) < (b) for DtS & SoD at T2 & T3.
Ussher and colleagues (2006) Abstinence: mean = 17.3 hrs.	Parallel arm design. Measures pre (T1), post (T2), 5 min (T3), 10 min (T4), 15 min (T5) & 20 min post treatment (T6). BaselineSoD = 4.7. Baseline DtS = 4.9*. *Only SoD reported in the article.*	All 5 min. (a) seated isometric exercise. (b) seated body scanning. (c) passive control.	33 M & 27 F. N = 20 in each group. Mean age = 32.2 yrs. Mean FTCD = 3.9. Mean CPD = 18.8.	(a) < (c) for SoD at T2 & T3. No difference between (b) & (c) at any point. *Both (b) & (c) as control conditions in the MA*
Taylor and Katomeri (2007)	Parallel arm design. Measures pre (T1), mid (T2), post (T3) treatment,	All 15 min & 2 min warm up. (a) self-paced brisk walk	Moderately active, 26 M & 34 F. Mean age = 28.6	Results reported as SoD & DtS change scores (from baseline)

Abstinence: min of 2 hrs.	pre (T4) & post (T5) Stroop task, pre (T6) & post speech task (T7), pre (T8) & post (T9) lit cig. BaselineSoD = 4.4. Baseline DtS = 5.1.	@ mean RPE = 10.9, mean HRR = 24.1%,N = 31. (b) passive control, N = 29.	yrs. Mean FTCD = 3.5. Mean CPD =1 4.9.	(a) > (b) for DtS & SoD at T2-T9. (a) attenuated responses to lit cig for SoD at T9.
Everson and colleagues (2008) Abstinence: mean = 17 hrs.	Parallel arm design. Measures pre (T1), mid (T2), 5min. (T3), & 30 min post treatment (T4). BaselineSoD = 4.6.	All 10 min. (a) cycling @ RPE = 14.8, HR = 155bpm, HRR = 68%. (b) cycling @ RPE = 12.5, HR = 131 bpm, HRR = 50%. (c) passive control.	Inactive, 25 M & 20 F. N = 15 in each group. Mean age = 21.8 yrs. Mean FTCD = 3.4. Mean CPD = 13.6.	(a & b) < (c) for SoD at T2 & T3. *Both (a) & (b) as exercise condition in the MA*.
Janse Van Rensburg and Taylor (2008) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), mid (T2), 5 min post (T3), 10 min. (T4) & 15 min post treatment (T5). Baseline DtS = 5.0. QSU-brief.	Both 15 min. (a) self-paced brisk walk @ mean RPE = 10.8 & mean HR = 113 bpm + 2 min warm-up & 1 min. cooldown. (b) passive control.	15 M & 8 F. Mean age = 23.1 yrs. Mean FTCD = 3.4. Mean CPD = 13.7. Mean SY = 7.0 yrs.	(a) < (b) for DtS at T2-T4. (a) < (b) for QSU-brief at T3-T5.
Ussher and colleagues (2009)	Parallel arm design Measures pre (T1), post (T2), 5 min (T3), 10 min (T4, not in normal environment) & 30 min post treatment (T5). On the same day: lab	All 10 min, mp3 instructions. (a) seated isometric exercise, N = 14. (b) body scan, N = 18. (c) passive control (audio recording), N = 18.	31 M & 17 F. Mean age = 27.8 yrs. Mean FTCD = 5.0. Mean CPD = 15.5. Mean SY = 11 yrs.	Lab settings: (a & b) < (c) for SoD at T3, T4 & T5 and (b) < (c) at T2. Normal environment: (a & b) < (c) for SoD at T2 & T3.

Abstinence: mean = 16.7 hrs.	settings followed with normal environment. Baseline SoD = 5.3.			*Both (b) & (c) as controls in the MA*. *Only lab settings results included in the MA.*
Janse Van Rensburg and colleagues (2009a) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), mid (T2), post treatment (T3), & post eye-tracking protocol (T4). Baseline DtS = 5.3.	All 15 min (a) cycling @ RPE = 11-13 and 2 min warm-up & 1 min cool-down. (b) passive control.	15 M & 5 F. Mean age = 29.1 yrs. Mean FTCD = 4.0. Mean CPD = 15.6. Mean SY = 15.1 yrs.	(a) < (b) for DtS at T2 &T3.
Janse Van Rensburg *et al.* (2009b) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), mid (T2), & post treatment (T3). Baseline DtS = 4.6.	All 10 min (a) cycling @ RPE=11-13, mean HR = 136 bpm & 2 min warm-up. (b) passive control.	10 participants. Age = 18-50 yrs. Mean FTCD = 3.4. Mean CPD = 13.7. Mean SY = 8.1 yrs.	Found significant condition (2) by time (3) interaction, but no post hoc tests reported.
Katomeri (PhD thesis 2009) Abstinence: required = 2 hrs.	Cross-over design. Measures pre (T1), mid (T2) & post treatment (T3) and pre (T4) & post (T5) smoking cue. BaselineSoD = 5.2*. Baseline DtS = 5.2*. Time to next cig.	All 15 min. (a) self-paced treadmill walk @ mean RPE = 12,2 mean HRR = 37,3%. (b) passive control.	Moderately active, 17 M & 13 F. Mean age = 21.9 yrs. Mean CPD = 13.7. Mean FTCD = 3.5.	(a) < (b) for DtS & SoD at T1 & T2. (a) > (b) for change in DtS in response to smoke cue (T5). (a) < (b) for time to next cig.

Thompson (MSc Dissertation, 2009) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), & post video (T2), mid (T3), post treatment (T4) & post second video (T5). Baseline SoD = 2.3. Baseline DtS = 2.4. *Cravings reported on a 6-point scale; scores were extrapolated to 7-point scale and used in the MA.*	All 15 min (2 min warm-up). (a) run @ mean HR = 160 bpm, mean RPE = 16.0. (b) brisk walk @ mean HR = 127 bpm, mean RPE = 11.8. (c) passive control.	5 M & 5 F. Mean age = 23.1yrs. Mean FTCD = 4.2.	(a) & (b) <(c) for DtS &SoD at T4. (a) < (c) for DtS at T3, T5 & for SoD atT3. (b) < (c) for SoD at T3 & T5. Decrease in cravings (vs. baseline): (a) for DtS at T3-T5 and for SoD at T3,T4. (b) for SoD at T3. *Both (a) & (b) as exercise condition in the MA*.
Faulkner and colleagues (2010) Abstinence: min of 3 hrs; mean = 8 hrs.	Cross-over design. Measures pre (T1), mid (T2), post (T3), 10 (T4) & 20 min post treatment (T5). BaselineSoD = 4.6*. Baseline DtS = 5.4. *Only DtS reported in the article.*	All 10 min. Screening session first. (a) brisk walk @ mean HR = 116 bpm, mean RPE = 11.9. (b) passive control.	11 M & 8 F. Mean age = 24.6 yrs. Mean FTCD = 4.5. Mean CPD = 15.2.	(a) < (b) for DtS in T2. (a) > (b) time to first puff. When controlled for duration of abstinence, both results no longer sig.
Scerbo and colleagues (2010) Abstinence: min of 3 hrs, mean = 4.8 hrs.	Cross-over design. Measures pre (T1), mid (T2), post (T3), 10 (T4), 20 (T5) & 30 min post treatment (T6). BaselineSoD = 5.5. Baseline DtS = 5.3.	All 15 min: (a) treadmill running @ 80-85% HRR, mean RPE = 16.2 (b) walking @ 45-50% HRR, mean RPE = 13.4. (c) passive control.	Moderately active, 10 M & 8 F. Mean age = 26 yrs. Mean FTCD = 4.4. Mean CPD = 13.9.	(a & b) < (c) for SoD at T2 & T3. (a) < (c) for SoD at T4 & T5. (a & b) < (c) for DtS at T2 & T3. (a) < (c) for DtS at T4. (b) < (c) for DtS at T5. *Both (a) & (b) as exercise condition in the MA*.

Janse Van Rensburg and colleagues (2012) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), mid (T2) & post treatment (T3). BaselineSoD = 5.1*. Baseline DtS = 5.3.	All 10 min: (a) cycling @ mean HR = 125 bpm, mean RPE = 12.6. (b) passive control.	20 M & F. Mean age = 20.3 yrs. Mean FTCD = 2.3. Mean CPD = 12.3. Mean SY = 4.5 yrs.	(a) < (b) for SoD & DtS at T2 &T3.
Oh and Taylor (2014) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), mid (T2), post (T3) & 5 min post treatment (T4). BaselineSoD = 2.5*. Baseline DtS = 2.5*.	All 15 min: (a) cycling @ mean HR = 165 bpm, mean RPE = 16.7 (b) cycling @ mean HR = 129 bpm, mean RPE = 13.7. (c) passive control.	Regular snackers, 15 M & 8 F. Mean age = 24 yrs. Mean FTCD = 2.8. Mean CPD = 13.0.	(a) & (b) < (c) for DtS & SoD at T1-T4. (a) < (c) for DtS & SoD at T4. *Both (a) & (b) as exercise condition in the MA*.
Janse Van Rensburg (unpublished) Abstinence: min of 15 hrs.	Cross-over design. Measures pre (T1), mid (T2), post treatment (T3) & post ERP (T4). Baseline DtS = 4.8*.	All 15 min: (a) cycling (RPE = 11-13). (b) passive control.	9 M & 4 F. Mean age = 22.5yrs. Mean FTCD = 2.3. Mean SY = 7.2 yrs.	NA
Haasova and colleagues (unpublished) Abstinence: min of 3 hrs; mean = 13.1 hrs.	Cross-over design. Measures pre (T1), post treatment (T2), post (T3) & 5 min post eye-tracking protocol (T4). BaselineSoD = 4.5*. Baseline DtS = 4.6*.	All 10 min. (a) brisk walk @ mean HR = 105.2 bpm, mean RPE = 11.8. (b) seated isometric exercise. (c) passive control (audio recording).	M & F. Mean age = 30.9 yrs. Mean FTCD = 3.4. Mean CPD = 17.1. Mean SY= 2.5 yrs.	(a) & (b) < (c) for SoD at T2. (b) < (c) for SoD at T3. No difference between (a) & (b) at any point. *Both (a) & (b) as exercise condition in the MA*.

Notes: All values are mean values across all treatment conditions (as reported in the individual articles, * indicates values not reported in articles): bpm = beats per minute, cig = cigarettes, CPD = cigarettes per day, DtS = Desire to Smoke, ESR = Evening Symptom report (Hughes and Hatsukami 1986), ERP= Event Related Potentials, F= females, FTCD = Fagerström Test for Cigarette Dependence (Fagerström 1978; 2012), M = males, N = number of participants, NA = not available, HR = heart rate, HRmax = age predicted heart rate max, HRR = heart rate reserve, QSU-brief = Questionnaire of Smoking Urges brief (Cox et al. 2001), RPE = Rate of Perceived Exertion, SoD = Strength of Desire to smoke, SJWS = Shiffman Jarvik Withdrawal Scale (Shiffman and Jarvik 1976), SY = Smoking Years (number of years spend smoking).

Table 57. Summary of studies excluded from quantitative synthesis

Study (in chronological order)	Design & cravings measures	Interventions	Subjects	Cravings related findings & exclusion reasons
Mikhail (MSc Dissertation, 1983) Abstinence: 30 min.	Cross-over design. Measures 1 h in lab post treatment + 23 hrs post lab, 60 min of surreptitious observation. Time to 1st cig. Time lit & number of puffs. Cig in follow up.	All 10 min plus 4-5 min cool down for (a) & (b). (a) cycling @ mean HR = 104 bpm, mean HRmax = 66-69% (b) cycling @ mean HR = 120 bpm, mean HRmax = 82-85%. (c) passive control.	Inactive, 18 M. Mean age = 26 yrs. Mean SY = 10 yrs. Smoked ≥ 1 pack/day for 3 years.	(a) & (b) < (c) time with 1st lit cig. No difference between (a) & (b). No other sig. differences. No self-report cravings measures & only 30 min abstinence period.
Reeser (MSc Dissertation, 1983) Abstinence: none prescribed, but mean = 30 min.	Parallel arm design. Two same sessions; 30 min of surreptitious observation. Time to 1st cig. Time lit & number of puffs. Time to cig after leaving.	All 20 min. (a) 3 min. stretching & 13 min cycling @ mean HR = 140 bpm, 60% max HR and 2 min cool down & 2 min stretching. (b) stretching & isometrics. (c) passive control.	Inactive, 25 F & 12 M. Mean age = 24 yrs. mean CPD = 23. Mean SY = 8.4 yrs. Smoked ≥ 1 pack/day for 2 yrs.	Data averaged from 2 sessions: (b) < (c) on number of puffs. (b) > (c) on time to 1st cig. 28% in (a) & (b) and 15% in (c) didn't smoke during observations. No self-report cravings measures & only 30 min abstinence period.
Pomerleau and colleagues (1987) Abstinence: 30 min.	Cross-over design. Measures 20 min pre & 20 min post treatment. SJWS, nicotine intake.	Both 30 min. (a) cycling @ 80% VO_2 max. (b) cycling @ 30% VO_2 max.	Inactive healthy, 10 M Mean age = 24.2 yrs. Mean CPD = 28.5. Mean SY = 8.3yrs.	No difference between (a) & (b) at any point. Different cravings measures & only 30 min abstinence period.

Thayer and colleagues (1993) Abstinence: 45 min.	Cross-over design. Measures pre & 20 min post treatment. Urge to smoke (7 point Likert scale) & time to next cig.	5 min all. (a) brisk walk. (b) passive control.	5 M & 11 F. Age = 18–44 yrs. Smoked 1- 2 packs per day.	(a) reduced urge to smoke & time to next cig (17 or 9 min delay). Only 45 min abstinence period.
Bock and colleagues (1999) Abstinence: during smoking cessation.	Cross-over design. Measures pre-post exercise/control. Study 1 (no control condition) Study 2 (as study 1, but with control condition) ESR.	All 30-40 min. (a) brisk walk @ mean HRR = 60-85% HRR, Study 1 & 2. (b) passive control , Study 2 . All participants involved in 11 weeks trial.	Inactive, Study 1 = 24 F. Study 2 = 44 F & 18 F controls. Mean age = 38.6 yrs. Mean CPD = 21.2. Mean SY = 22.1. Mean FTCD = 4.5.	(a) Study1 & 2 reduced nicotine withdrawal and cig cravings, in all weeks, (5-10) after quit day. Different cravings measures, no control group (Study 1) & during smoking cessation.
Daley and colleagues (2004) Abstinence: approximately 17 hrs.	Parallel arm design. Measures pre (T1), post (T2), 30min. (T3), & 60 min post treatment (T4). SJWS.	Both for 30 min. (a) cycling @ HRmax = 60-65% (b) passive control (video on smoking cessation).	Sedentary 16 M & F. Mean age = 21 yrs. Mean CPD = 12.7. Mean SY = 5.5 yrs.	No differences between (a) & (b) at any time point. Different cravings measures.
Daniel (Study 3b PhD Thesis, 2005)	Parallel arm design. Measures 10 (T1), 5 min pre (T2) & pre exercise	All 10 min cycling @ 40-60%HRR plus 1-2 min warm-up.	N = 40. Mean age = 24.3 yrs.	Groups analysed together: decrease in DtS &SoD in comparison to baseline at T4, T5, T6 & T7.

Abstinence: 11-15 hrs.	(T3), mid (T4) & post exercise (T5) & 5 post (T6) & 10 min post exercise (T7). BaselineSoD = NA. Baseline DtS = NA.	Groups based on motivation to smoke: high and low.	CPD =14.6. FTCD = 4.2 (sig difference between groups).	No difference between groups at any point. No control group.
Everson and colleagues (2006) Abstinence: mean = 17.2 hrs.	Parallel arm design. Measures pre (T1), mid (T2), 5 min (T3), & 30 min post treatment (T4). BaselineSoD = 4.9.	All 10 min. (a) cycling @ mean RPE = 12.3, mean HR = 112 bpm, mean HRmax = 55%. (b) cycling control @ mean RPE = 8.3, mean HR = 89 bpm, mean HRmax 44%.	Less active, 19 M & 18 F. N = 18 in each group. Mean age = 17.7 yrs. Mean CPD = 13.6.	No differences between groups at any time point. No control group.
Daniel and colleagues (2007) Abstinence: mean = 13 hrs.	Parallel arm design. Measures pre (mean of 10, 5 & 0 min pre), during (mean of mid and end of treatment) & post treatment (mean of 5 & 10 min post). BaselineSoD = 4.4. Baseline DtS = 4.6.	All 10 min, cycling @ mean HRR = 40-60%, mean RPE = 13.4 + 1-2 min warm-up. 3 groups: positive, negative and neutral expectation of effects of exercise.	Sedentary, 22 M & 23 F. Mean age = 24 yrs. Mean FTCD = 4.2. Mean CPD = 14.4. Mean SY = 7.4 yrs.	All groups reduced SoD & DtS from pre to during & post exercise. No difference between groups at any point. No control group.
Katomeri (Study 4 PhD Theses, 2009) Abstinence:	Cross-over design. Measures pre, mid & post exercise + pre & post cig cue.	(a) 15 min. self-paced walk @ mean HRR = 30.79%, mean RPE = 11.62). (b) passive control.	19 M &11 F. Mean age = 25.8 yrs. Mean FTCD = 3.8.	(a) for cravings sig lower scores (in comparison to baseline) at all measurement points. (a) > (b) for time to next cig.

none.	BaselineSoD = NA. Baseline DtS = 2.8.		CPD = 15.6.	No abstinence period.
Williams and colleagues (2010) Abstinence: during smoking cessation.	Parallel arm design. Measures pre (T1), post treatment (T2) & at next destination (T3). 5 items questionnaire, (0-100 scale).	(a) 50 min brisk walk (3 x per week) over 8 weeks. (b) 30 min watching films (3 x per week) over 8 weeks.	Low active 60 F. Mean age = 42.4 yrs. Mean FTCD = 4.8.	No differences between groups at any time point. Use of nicotine replacement therapy, different cravings measures & during smoking cessation.
Elibero and colleagues (2011) Abstinence: 1 hour.	Parallel arm design. Measures pre (T1), post (T2) & 20 min post treatment (T3). QSU-brief.	All 30 min (a) walking. (b) Hatha yoga. (c) passive control.	48 M & 28 F Mean age = 28.9 yrs. Mean FTCD = 4.6. CPD = 19.8. Mean SY = 12.5 yrs.	No significant group by time interactions. When two condition compared directly: (a) & (b) < (c) for QSU brief-global & Factor 1. Different cravings measures & only 1 hour abstinence period.
Arbour-Nicitopoulos and colleagues (SRNT, 2011) Abstinence: minimum of 3 hrs.	Cross-over design. Measures pre (T1), mid (T2), post (T3), 10 min (T4) & 20 min post treatment (T5). Baseline DtS = NA.	All 10 min. (a) brisk walk @ mean RPE = 7.1. (b) passive control. Screening session first.	Severe mental illness & inactive 6 M & 8 F. Mean age = 50.1 yrs. Mean FTCD = 4.7. CPD = 10.2.	No differences between groups at any time point. Use of nicotine replacement therapy and all participants were trying to quit smoking.
Janse van Rensburg and colleagues (SRNT, 2011)	Parallel arm design. Measures pre (T1), post treatment (T2) & 25 min post (T3).	All 20 min. (a) exercise @ HRR = 75%. (b) exercise @ HRR = 40%.	162 M & F Mean age = 30.8 yrs. Mean FTCD =	(a) & (b) < (c) in factor 1 & 2 of QSU-brief. No diff between (a) & (b) at any point or any measure.

Abstinence: overnight.	QSU-brief.	(c) passive control.	4.4. CPD = 18.0.	Different cravings measures & data not available.
Harper and colleagues (2012)[a] Abstinence: during smoking cessation.	Cross-over design. 14 weeks exercise programme, week 4 = quit week. Acute ex. sessions & measures at week 5 (T1), week 7 (T2) and week 10 (T3). SJWS.	All 20 min. Choice of treadmill, rowing, stair climber & bike. (a) vigorous intensity @ HRR > 70%. (b) moderate intensity @ HRR = 50-60%. Not all complied with intensities.	119 F. Mean age = 40.6 yrs. Mean FTCD = 5.7. CPD = 16.8. Mean SY = 22.1 yrs.	Results were presented as pre & post exercise cravings scores for each week and a sig reduction in cravings was found in all acute sessions (T1-T3). No control group. Different cravings measures, use of NRT & during smoking cessation.
Harper and colleagues (2013)[a] Abstinence: during smoking cessation.	Cross-over design. 14 weeks exercise programme week 4 = quit week. Acute ex. sessions & measures at week 5 (T1). SJWS.	All 20 min. Choice of treadmill, rowing, stair climber & bike. (a) moderate intensity @ HRR = 50-60%.	58 F. Mean age = 42.7 yrs. Mean FTCD = 5.0. CPD = 17.8. Mean SY = 22.5 yrs.	Results were presented as pre & post exercise cravings scores and a sig reduction in cravings was found at T1. No control group. Different cravings measures, use of NRT & during smoking cessation.
Ho and colleagues (2014) Abstinence: approximately 16-18 hrs.	Cross-over design. Measures pre, post & 30 min post treatment. During 24- hrs smoking abstinence trials. SoD (6 points scale)	All 20 min. (a) 6 whole body resistance exercises; 3 sets of 10 repetitions (b) passive control.	Sedentary 8 M. Mean age = 20.1 yrs. Mean SY = 2.9 yrs.	No differences between (a) and (b). Significant main effect of time with SoD increasing over time. No IPD available.

Notes: All values are mean values across all treatment conditions (as reported in the individual articles, * indicates values not reported in articles): bpm = beats per minute, cig = cigarettes, CPD = cigarettes per day, DtS = Desire to Smoke, F= females, FTCD = Fagerström Test for Cigarette Dependence (Fagerström 2012), M = males, N = number of participants, NA = not available, NRT = nicotine replacement therapy, HR = heart rate, HRmax = age predicted heart rate max, HRR = heart rate reserve, QSU-brief = Questionnaire of Smoking Urges brief (Cox et al. 2001), RPE = Rate of Perceived Exertion, SoD = Strength of Desire to smoke, SJWS = Shiffman Jarvik Withdrawal Scale (Shiffman and Jarvik 1976), SY = Smoking Years (number of years spend smoking), T = time, 5 items questionnaire (Shiffman et al. 2003), a = published data includes more participants than thesis, results presented for participants included in thesis.

Appendix F; Chapter 6: The acute effects of physical activity on cigarette cravings: Exploration of potential moderators, mediators and physical activity attributes using systematic review and individual participant data meta-analyses

Table 58. Strength of desire; physical activity attributes combinations investigated in randomised controlled trials

Intensity	*Duration*	*Type*	*Number of studies*	*Number of participants*
light	short	isometric	1	20
		cycling	1	28
	medium	isometric	2	34
moderate	short	cycling	1	28
	medium	walking/running	2	43
		cycling	4	94
	long	walking/running	5	104
		cycling	3	23
vigorous	medium	cycling	1	15
	long	walking/running	2	28
		cycling	1	23

Table 59. Desire to smoke; physical activity attributes combinations investigated in randomised controlled trials

Intensity	*Duration*	*Type*	*Number of studies*	*Number of participants*
light	short	isometric	1	20
		cycling	1	28
	medium	isometric	2	20
moderate	short	cycling	1	28
	medium	walking/running	2	43
		cycling	4	90
	long	walking/running	6	127
		cycling	3	56
vigorous	long	walking/running	2	28
		cycling	1	23

Table 60. Strength of desire; Associations of covariates and the effects of physical activity on the cigarette cravings.

Covariates		Number of observations	Number of studies	Mean difference (95%CI) 0-100 scale	p-value
Gender (male = reference group)		704	12	2.04 (-1.57, 5.65)	0.268
CO (ppm)		467	8	0.30 (-0.23, 0.84)	0.265
PA level (inactive = reference group)		536	9	-4.97 (-12.83, 2.89)	0.215
FTCD		737	15	0.42 (-0.47, 1.31)	0.356
Abstinence Period (hours)		504	9	0.10 (-0.22, 0.42)	0.545
Baseline FS[1]		312	6	-0.08 (-1.40, 1.55)	0.920
Baseline FAS[1]		312	6	3.01 (0.79, 5.23)	0.008
Resting heart rate (bpm)		430	9	0.3 (0.02, 0.52)	0.034
Smoking years		441	8	-0.41 (-0.65, -0.18)	0.001
BMI (kg/m^2)		574	10	0.90 (0.32, 1.48)	0.002
Age (years)		731	13	-0.36 (-0.56, -0.15)	0.001
BMI & age	BMI	574	10	1.17 (0.57, 1.76)	< 0.001
	Age			-0.42 (-0.66, -0.17)	0.001

Notes: Each covariate is fitted individually with intervention (adjusted for study) in one-stage IPD meta-analyses. The results of the most appropriate model, including age and BMI in the same analysis, are also included. DtS substituted by SoD where no DtS scores were available, 1 = the combined cravings measure consists of DtS only. BMI = body mass index; FAS = felt arousal scale; FS = feeling scale; FTCD = Fagerström Test of Cigarette Dependence.

Table 61. Desire to smoke; Associations of covariates and the effects of physical activity on the cigarette cravings

Covariates		Number of observations	Number of studies	Mean difference (95%CI) 0-100 scale	p-value
Gender (male = reference group)		676	12	0.86 (-2.78, 4.50)	0.643
CO (ppm)		437	8	0.30 (-0.20, 0.79)	0.237
PA level (inactive = reference group)		491	8	0.19 (-7.12, 7.50)	0.959
FTCD		776	13	0.13 (-0.70, 0.96)	0.760
Abstinence Period (hours)		411	7	0.10 (-0.22, 0.41)	0.548
Baseline FS[1]		378	8	-0.52 (-1.84, 0.81)	0.443
Baseline FAS[1]		378	8	0.72 (-1.35, 2.80)	0.495
Resting heart rate (bpm)		432	9	0.21 (-0.02, 0.45)	0.070
Smoking years		409	8	-0.35 (-0.56, -0.14)	0.001
BMI (kg/m^2)		529	9	0.86 (0.27, 1.45)	0.004
Age (years)		703	13	-0.27 (-0.47, -0.07)	0.008
BMI & age	BMI	529	9	1.05 (0.44, 1.66)	0.001
	Age			-0.27 (-0.51, -0.04)	0.025

Notes: Each covariate is fitted individually with intervention (adjusted for study) in one-stage IPD meta-analyses. The results of the most appropriate model, including age and BMI in the same analysis, are also included. DtS substituted by SoD where no DtS scores were available, 1 = the combined cravings measure consists of DtS only. BMI = body mass index; FAS = felt arousal scale; FS = feeling scale; FTCD = Fagerström Test of Cigarette Dependence.

Table 62. Strength of desire; Associations of change in affect (FS/FAS) and the effects of physical activity on cigarette cravings, using separate one-stage IPD meta-analyses for each covariate.

Covariates	Number of observations	Number of studies	Mean difference (95%CI) 0-100 scale	p-value
Change in FS	307	8	-0.11 (-0.28, 0.06)	0.198
Change in FAS	307	8	0.06 (-0.05, 0.18)	0.290
Change in FS (moderate intensity PA only)	253	8	-0.12 (-0.32, 0.08)	0.248
Change in FAS (moderate intensity PA only)	253	8	0.07 (-0.07, 0.20)	0.347

Notes: DtS = desire to smoke; FAS = felt arousal scale; FS = feeling scale; PA = physical activity; SoD = strength of desire.

Table 63. Desire to smoke; Associations of change in affect (FS/FAS) and the effects of physical activity on cigarette cravings, using separate one-stage IPD meta-analyses for each covariate.

Covariates	Number of observations	Number of studies	Mean difference (95%CI) 0-100 scale	p-value
Change in FS	372	8	-0.13 (-0.29, 0.02)	0.091
Change in FAS	373	8	0.07 (-0.04, 0.18)	0.196
Change in FS (moderate intensity PA only)	318	8	-0.13 (-0.32, 0.05)	0.165
Change in FAS (moderate intensity PA only)	319	8	0.09 (-0.04, 0.21)	0.174

Notes: DtS = desire to smoke; FAS = felt arousal scale; FS = feeling scale; PA = physical activity; SoD = strength of desire.

Table 64. Strength of desire; The effects of physical activity attributes on cigarette cravings: separate one- stage meta-analyses of the effects of duration, type and intensity

PA characteristics	Categories	Mean difference 0-100 scale (95%CI)	p-value
Duration	Short	-11.26 (-18.90, -3.62)	0.004
	Medium	-30.26 (-48.42,-12.09)	0.001
	Long	-40.06 (-51.92, 28.20)	< 0.001
Type	Isometric	-8.49 (-15.52, -1.47)	0.018
	Walking/running	-35.09 (-48.31,-21.87)	< 0.001
	Cycling	-36.06 (-54.30, 17.83)	< 0.001
Intensity	Light	-6.47 (-12.37, -0.58)	0.031
	Moderate	-36.115 (-46.57,-25.26)	< 0.001
	Vigorous	-30.48 (-36.88, 24.86)	< 0.001

Notes: One-stage IPD meta-analyses (adjusted for baseline cravings), with a fixed effect on study, random intercept on participant, comparing PA categories against control participants. Models had random effects applied to medium and long duration categories, to walking/running and cycling type categories, and to moderate intensity category. Negative ES for cravings measures favours intervention, and positive ES favours control condition. CI=confidence interval; IPD = individual participant data; PA = physical activity.

Table 65. Desire to smoke; The effects of physical activity attributes on cigarette cravings: separate one- stage meta-analyses of the effects of duration, type and intensity

PA characteristics	Categories	Mean difference 0-100 scale (95%CI)	p-value
Duration	Short	-12.74 (-35,83, 10.34)	0.279
	Medium	-36.87 (-53.41, -20.33)	< 0.001
	Long	-36.54 (-46.28, -26.79)	< 0.001
Type	Isometric	-6.44 (-14.99, 1.91)	0.131
	Walking/running	-34.62 (-47.32, -21.92)	< 0.001
	Cycling	-37.06 (-48.14, -25.98)	< 0.001
Intensity	Light	-10.37 (-17.03, -3.72)	0.002
	Moderate	-35.46 (-39.63, -24.80)	< 0.001
	Vigorous	-32.22 (-39.63, -24.80)	< 0.001

Notes: One-stage IPD meta-analyses (adjusted for baseline cravings), with a fixed effect on study, random intercept on participant, comparing PA categories against control participants. Models had random effects applied to short, medium and long duration categories, to walking/running and cycling type categories, and to moderate intensity category. Negative ES for cravings measures favours intervention, and positive ES favours control condition. CI = confidence interval; IPD = individual participant data; PA = physical activity.

Appendix G; Chapter 7: How habitual physical activity and other individual characteristics influence cigarette cravings, an exploration of baseline measures from the Exercise Assisted Reduction then Stop smoking study

Table 66. Cravings, withdrawal symptoms and mood measures

Measure	Details
MPSS	Participants answered the following question: "Please show for each of the items below how you have been feeling over the past week". The questionnaire used a 1−5 point response range, from "not at all" to "extremely". There were nine MPSS subscales: restless, irritable, depressed, hungry, poor concentration, poor sleep at night, stressed out and tense.
EQ-5D-3L	The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems.
PSS	Measures the extent to which respondents have felt their life to be stressful during the past month. They rate four following statements using a 5−point scale (0 = never to 4 = very often): "I have been unable to control the important things in my life", "I have felt confident about my ability to handle personal problems", "I have felt that things are going my way" and "Difficulties are piling up so high that I cannot overcome them".

Notes: EQ-5D-3L = three level European Quality of Life-5 Dimension questionnaire; MPSS = Mood and Physical Symptoms Scale; PSS = Perceived Stress Scale.

Alcohol consumption post hoc analyses; "Alcohol drinking frequency"

Table 67 Strength of Urges; results of linear regression models including frequency of *"Alcohol drinking frequency"*

"Alcohol drinking frequency" **(N = 99)**	**Mean difference (95% CI)**	**t statistics (p)**
Once a month or less	-25.08 (-39.28; -10.88)	-3.51 (0.001)
Two to four times a month	-17.38 (-31.58; -3.19)	-2.43 (0.017)
Two to three times a week	-20.00 (-34.96; -5.04)	-2.65 (0.009)
Four or more times a week	-30.33 (-47.29; -13.37)	-3.55 (0.001)
F statistic	$F_{(4,94)} = 4.11$; p = 0.004	
R^2	0.149	

Notes: "Not drinking alcohol" was the baseline category; 95 % CI = 95% Confidence Interval; N = number of participants.

Table 68. Strength of Urges; results of linear regression models including "*Drinking alcohol*" (a binary dividing participants into "drinking alcohol" and "not drinking alcohol" subpopulations based on participants' responses to the *"Alcohol drinking frequency"*)

"Drinking alcohol" **(N = 99)**	**Mean difference (95%CI)**	**t statistics (p)**
Drinking alcohol	-22.24 (-34.54; -9.94)	-3.59 (0.001)
F statistic	$F_{(1,97)} = 12.87$; p = 0.001	
R^2	0.117	

Notes: "Not drinking alcohol" was the baseline category; 95 % CI = 95% Confidence Interval; N = number of participants.

Alcohol consumption post hoc analyses; "Drinks on a typical day"

Table 69 Strength of Urges; results of linear regression models including frequency of *"Drinks on a typical day*

"Drinks on a typical day" **(N = 84)**	**Mean difference (95% CI)**	**t statistics (p)**
3 or 4 drinks	1.65 (-11.38; 14.68)	0.25 (0.801)
5 or 6 drinks	1.54 (-12.10; 15.17)	0.22 (0.823)
7 to 9 drinks	15.65 (1.51; 29.80)	2.20 (0.031)
10 or more drinks	17.87 (1.12; 34.63)	2.12 (0.037)
F statistic	$F_{(4,79)} = 2.28$; p = 0.068	
R^2	0.104	

Notes: "1 or 2 drinks" was the baseline category; 95 % CI = 95% Confidence Interval; N = number of participants.

Table 70. Strength of Urges; results of linear regression models including *"Light and heavy drinkers*" (a binary dividing participants into "light" and "heavy drinkers" subpopulations based on participants' responses to the *"Drinks on a typical day"*)

"Light and heavy drinkers" **(N = 84)**	**Mean difference (95%CI)**	**t statistics (p)**
Heavy drinkers	15.50 (5.39; 25.61)	3.05 (0.003)
F statistic	$F_{(1,82)} = 9.31$; p = 0.001	
R^2	0.102	

Notes: "Light drinkers" was the baseline category; 95 % CI = 95% Confidence Interval; N = number of participants.

Alcohol consumption post hoc analyses; combining "Alcohol drinking frequency" and "Drinks on a typical day": three levels "Alcohol consumption" variable ("never, light/moderate and heavy drinkers")

Table 71 Strength of Urges; results of linear regression models including frequency of *"Alcohol consumption"*

""Alcohol consumption" **(N = 99)**	**Mean difference (95% CI)**	**t statistics (p)**
Light/moderate drinkers	-26.67 (-39.28; -10.88)	-4.35 (< 0.001)
Heavy drinkers	-11.17 (-31.58; -3.19)	-1.60 (0.114)
F statistic	$F_{(2,96)} = 11.54$; $p < 0.001$	
R^2	0.194	

Notes: "Not drinking alcohol" was the baseline category; 95 % CI = 95% Confidence Interval; N = number of participants.

Predictors of Strength of Urges

Table 72. Series of linear regression models investigating the effects of each potential additional predictor individually on strength of urges (not adjusted for moderate intensity physical activity, N = 99)

		Strength of Urge	
Predictors		Mean difference (95% CI)	t statistics (p)
EQ-5D-3L		-14.99 (-31.86; 1.88)	-1.76 (0.081)
PSS		1.21 (0.10; 2.33)	2.16 (0.033)
MPSS		8.72 (3.67; 13.78)	3.43 (0.001)
FTCD		3.65 (1.46; 5.85)	3.31 (0.001)
mCEQ reward		5.43 (1.75; 9.12)	2.93 (0.004)
"Alcohol consumption"[a, b] (N=98)	Light drinkers	-26.67 (-39.28; -10.88)	-4.35 (< 0.001)
	Heavy drinkers	-11.17 (-31.58; -3.19)	-1.60 (0.114)
	Global F statistic of the three levels alcohol consumption[c]		$F_{(2,96)} = 11.54$; $p < 0.001$
"Drinks on a typical day"[d]	3 or 4 drinks	1.65 (-11.38; 14.68)	0.25 (0.801)
	5 or 6 drinks	1.54 (-12.10; 15.17)	0.22 (0.823)
	7 to 9 drinks	15.65 (1.510; 29.80)	2.20 (0.031)
	10 or more drinks	17.87 (1.12; 34.63)	2.12 (0.037)
	Global F statistic of the five levels alcohol consumption[c]		$F_{(4,79)} = 2.28$; $p = 0.068$
Employment status		8.52 (-0.75; 17.79)	1.82 (0.071)
Mental health[e]		12.56 (3.37; 21.75)	2.71 (0.008)
Met PA guidelines[b]		-5.86 (-16.07; 4.34)	-1.14 (0.257)
Gender		3.48 (-5.97; 12.93)	0.73 (0.466)

Notes: a = "not drinking alcohol" (no alcohol consumption), "light drinkers" (consuming between 1 and 6 alcoholic drinks on a typical day), and "heavy drinkers" (consumed 7 or more alcoholic drinks on a typical day); b = N = 98; c = p-values are derived from a Wald test; d = N = 83; e = answered 'moderately' or

‘extremely’ anxious or depressed to item 5 of the EQ-5D-3L questionnaire; “not drinking alcohol” was the baseline category for drinking alcohol; “male” was the baseline category for gender; “employed” was the baseline category for employment status; “not meeting PA guidelines” was the baseline category for Met PA guidelines; ”lack of anxiety” was the baseline category for anxiety present; BMI= body mass index (kg/m2); EQ-5D-3L = three level European Quality of Life-5 Dimension questionnaire; FTCD = Fagerström Test for Cigarette Dependence; mCEQ = modified Cigarette Evaluation Questionnaire; N = Number of participants; MPSS = Mood and Physical Symptoms Scale; PA= physical activity; PSS = Perceived Stress Scale.

Moderators of Strength of Urges

Table 73 Linear regression showing the five levels "Drinks on a typical day" moderator of Strength of Urges (adjusted for physical activity; in alcohol drinking sub-population, N = 84)

		Mean difference (95%CI)	t statistics (p)
Moderate intensity PA (minutes per day)		-0.16 (-0.32; -0.01)	-2.06 (0.043)
"Drinks on a typical day" [a]	Three to four	-1.46 (-18.85; 15.93)	-0.17 (0.868)
	Five to six	1.38 (-16.18; 18.93)	0.16 (0.876)
	Seven to nine	0.04 (-18.56; 18.65)	0.01 (0.996)
	Ten and more	4.35 (-17.45; 26.14)	0.40 (0.692)
PA /" Drinks on a typical day" interaction	PA/three to four	0.07 (-0.16; 0.25)	0.75 (0.458)
	PA/five to six	0.04 (-0.13; 0.22)	0.51 (0.613)
	PA/seven to nine	0.24 (0.04; 0.44)	2.39 (0.019)
	PA/ten and more	0.21 (-0.02; 0.43)	1.83 (0.071)
F statistic		$F_{(9,73)} = 3.15$; p = 0.003	
R^2		0.191	
Global F statistic of the five levels alcohol consumption[b]		$F_{(2,92)} = 0.08$; p = 0.987	
Global F statistic of the PA/ five levels alcohol consumption interaction[b]		$F_{(4,73)} = 2.63$; p = 0.041	

Notes: a = participants responses were divided into the five following categories: one or two drinks, three or four drinks, five or six drinks, seven to nine drinks, ten or more drinks; b = p-values are derived from a Wald test; "one or two drinks" was the baseline category for "How many drinks containing alcohol do you have on a typical day when you are drinking?"; 95 % CI = 95% Confidence Interval; PA = Physical Activity.

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