The LEAP trial: A randomised controlled trial of physical activity for smoking cessation in pregnancy, with economic evaluation

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Professors West, Coleman and Aveyard undertake research and consultancy for companies that develop and manufacture smoking cessation medications. All other authors have no declared competing interests

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with

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Abstract

559 words

Background

Smoking during pregnancy is the main preventable cause of poor birth outcomes, yet in the UK at least 12% of women smoke through their pregnancy. Improved methods are needed to help women to quit smoking during pregnancy. The evidence for physical activity (PA) programmes aiding smoking cessation is mixed. That said, pregnancy provides a compelling rationale for PA interventions as cessation medication is contraindicated or ineffective and an effective PA intervention could be highly cost-effective.

Objective

To examine the effectiveness and cost effectiveness of a PA intervention plus standard behavioural-support for smoking cessation relative to behavioural support alone for achieving biochemically-validated smoking cessation at end of pregnancy.

Design

Multicentre, two-group, pragmatic, randomised controlled trial and economic evaluation with follow-up at end-pregnancy and six months after birth. Randomisation was stratified by centre, and a computer-generated sequence was used to allocate participants using a 1:1 ratio.

Setting

13 hospitals offering antenatal care in the United Kingdom.

Participants

Women between 10 and 24 weeks gestation who smoked ≥5 daily cigarettes before and ≥1 during pregnancy.

Interventions

Eligible participants were individually randomized to either a control group (behavioural support for smoking cessation), or behavioural support plus a PA intervention, which consisted of supervised exercise on a treadmill plus PA consultations.

Main outcome measures

Primary outcome: Self-reported, continuous abstinence from smoking between a quit date and end of pregnancy, validated by measurement of expired carbon monoxide and/or salivary cotinine. Secondary outcomes: included maternal weight and depression, birth outcomes, withdrawal symptoms and urges to smokes. Economic: Costs of PA versus control interventions.

Results

789 women were randomised. Four were excluded post-randomization; two of these had been enrolled twice in sequential pregnancies and two were ineligible at their baseline visit and had been randomised erroneously. 785 participants were retained in the intention-to-treat analysis (PA n=392, control n=393). There was no significant difference in the rate of abstinence at the end of pregnancy between the PA and control group (7.7%, 6.4%, respectively; OR for PA group abstinence, 1.21; 95% CIs, 0.70 to 2.10). For PA group compared with the control group, there was a significantly greater percentage increase in self-reported minutes of moderate to vigorous intensity physical activity from baseline to one week of 40% (95% CI: 13%, 73%), to four weeks of 34% (6%, 69%) and to six weeks of 46% (12%, 91%) ($p<0.001$). At end of pregnancy these reports were still 29% (5%, 60%) higher in the PA group relative to the control group, and these reached statistical significance. However, relative to baseline in both groups, there was a decrease in self-reported physical activity of this intensity at the end of pregnancy and six months. There were no significant differences between the study groups for change in maternal depression or weight, withdrawal symptoms or urges to smoke. Adverse events and birth outcomes were similar in the two groups, except there were significantly more caesarean births in the control group than in the PA group (28.7% vs 21.3%, $p<0.023$).

The PA intervention was less costly than the control, by a margin of £35 per participant. This was mainly attributable to increased healthcare usage in the control group; however, as revealed in the scatterplot, there was considerable statistical uncertainty around this estimate.

Conclusions

During pregnancy, offering an intervention combining supervised exercise and PA counselling does not add to the effectiveness of behavioural support for smoking cessation.

Trial registration

Current controlled trials ISRCTN48600346

Funding

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List of figures and tables

List of abbreviations

AE(s)	Adverse event(s)
BCTs	Behaviour change techniques
BMI	Body mass index
CI	Confidence interval
CO	Carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
COT	Salivary cotinine
EQ-5D	European Quality of Life - 5 Dimensions
EOP	End of pregnancy
GP	General practitioner
GWG	Gestational weight gain
HTA	Health Technology Assessment programme
ICER	Incremental cost-effectiveness ratio
IOM	Institute of Medicine
ITT	Intention to treat
IQR	Interquartile range
LEAP	London Exercise and Pregnancy trial
MedDRA	Medical Dictionary for Regulatory Activities
MVPA	Moderate to vigorous intensity physical activity
NCTU	Nottingham Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NIHR	National Institute for Health Research
NRT	Nicotine replacement therapy
OR	Odds ratio
PA	Physical Activity
PAS	Patient Administration System
PCRN	NIHR Primary Care Research Network
PCT	Primary Care Trust
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
ppm	Parts per million
QALY	Quality Adjusted Life Years
RCT	Randomised controlled trial
RM	Research midwife
RR	Risk ratio
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SGUL	St George's University of London
SD	Standard deviation
SOP	Standard operating procedure
SSS	NHS Stop Smoking Service
TSC	Trial steering committee

Scientific summary

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Background

Maternal smoking in pregnancy is the main preventable cause of morbidity and death among women and infants. In most high-income countries at least 10% of women smoke during pregnancy and the prevalence is rising in low and middle income nations. There is evidence that behavioural support increases the rate at which women can stop smoking but there is no evidence that smoking cessation medication adds to this. The large majority of women who receive behavioural support for cessation during pregnancy do not manage to stop smoking and thus new options that add to the effectiveness of behavioural support are needed.

Physical activity programmes may add to the effectiveness of behavioural support. There is convincing evidence that PA reduces the intensity of urges to smoke in the general population of smokers, which are the main cause of relapse to smoking. In non-pregnant smokers, the trial evidence that PA programmes improve cessation rates is mixed, but most trials were small and had other design features that make the evidence hard to interpret. Moderate-intensity PA (e.g. brisk walking) is recommended during pregnancy, it has been shown to reduce cigarette cravings and pregnant smokers, especially those who are reluctant to use nicotine replacement therapy, are likely to be receptive to such an intervention. We conducted the **L**ondon **E**xercise **A**nd **P**regnant smokers (LEAP) trial to assess the effectiveness and cost effectiveness of a PA intervention for smoking cessation during pregnancy.

Objectives

The main objective of the study was to investigate whether behavioural support for smoking cessation in pregnancy plus a PA intervention is more effective than behavioural support alone, in achieving biochemically validated smoking cessation, between a quit date and end of pregnancy. A further objective was to assess the cost-effectiveness of the intervention for achieving smoking cessation at end of pregnancy.

Methods

The LEAP trial was a pragmatic, randomised, controlled trial with an accompanying health economic evaluation. Following their first antenatal booking visit, researchers identified pregnant smokers via lists on the computerised patient administration system at 13 hospital trusts, they discussed the study with potential participants via telephone, and enrolled women who consented to participate and met the inclusion criteria. We included women between 10

and 24 weeks pregnant, who smoked one or more cigarettes daily at trial entry and who had smoked at least five cigarettes daily before pregnancy. Participants set quit dates and researchers offered six weekly sessions of 20 minutes of individual-behavioural cessation support. At enrollment, participants were randomly assigned by the researcher to behavioural support alone, or to behavioural support plus a PA intervention that included 14 sessions of supervised exercise on a treadmill combined with nine PA consultations.

Researchers followed up participants at a visit at the end of pregnancy (valid if between 36 weeks gestation and 10 weeks after the birth) and by telephone at six months postnatally. Researchers retrieved birth outcome data from medical records. The primary outcome was self-reported continuous abstinence from smoking between the quit date and end of pregnancy validated by exhaled carbon monoxide (CO) and/or salivary cotinine. Temporary, brief smoking lapses of up to five cigarettes in total were permitted following the quit day. Secondary outcomes included validated abstinence at four weeks after the quit date and self-reported abstinence at six months postnatally. Self-reports of PA levels were collected at baseline and weeks one, four, and six after the quit date, at end of pregnancy and six months post-partum. To validate self-reported PA, a 10% random subsample of participants had PA objectively measured via an accelerometer. Ratings of withdrawal symptoms, urge to smoke, confidence for quitting smoking and confidence for taking PA were recorded. Changes in maternal depression were examined between baseline, end of pregnancy and six months after the birth. Changes in maternal weight were assessed between baseline and end of pregnancy. Maternal and fetal adverse events and birth outcomes were collected from hospital records.

Based on a systematic review, anticipated a cessation rate of 15% in the control group, on the basis that 9% of pregnant women who are smokers stop smoking with usual care after their first antenatal visit and an additional 6% to 7% quit with behavioural support. Based on pilot work, a cessation rate of 23% was projected in the treatment group. The aim was to recruit 866 participants, providing 83% power at a 5% significance level to detect an 8% absolute difference in the rate of the of smoking cessation at end of pregnancy between the two groups, corresponding to an odds ratio of 1.69. Analysis was on an intention-to-treat basis; participants with missing outcome data were assumed to be smoking. The proportion of women reporting continuous smoking abstinence at end of pregnancy was compared between study groups using logistic regression, with adjustment for recruitment centre. Economic analyses assessed the costs of delivering the interventions for each participant in the intervention versus control groups.

Results

789 women were enrolled in the trial. Four women were excluded post-randomisation, two because they were enrolled twice in sequential pregnancies and two were ineligible at their baseline visit and had been erroneously randomised. Of the 785 women (392 in PA group) included in the intention-to-treat analysis, there were 774 singleton births, 10 twins and one unknown as she withdrew consent. The follow-up rate for the primary outcome was 88.8%, and this was similar for the two study groups.

Adherence: Participants attended a median of four of 14 treatment sessions in the intervention group and three of six in the control group. Women in the intervention group increased their PA more than women in the control group. The percentage increase in minutes of moderate to vigorous intensity physical activity was 40%, (95% CI 13%, 73%) greater at one week, 34% (6%, 69%) greater at four weeks and 46% (12%, 91%) greater at six weeks ($p<0.001$). At end of pregnancy these reports were still 29% (95% CI: 5%, 60%) higher in the physical activity group relative to the control group, and the difference was statistical significant. However, there was a decrease in self-reported minutes of physical activity at the end of pregnancy and six months after the birth, relative to baseline, for both groups.

Smoking outcomes: There was no significant difference in smoking abstinence rates between the two groups. The rate of validated continuous abstinence at end of pregnancy was 7.7% in the PA group and 6.4% in the control group (OR for PA group, adjusted for centre only, 1.21; 95% CI, 0.70 to 2.10). At four weeks, the validated abstinence rate was 12.8% in the PA group and 15.5% in the control group (OR, adjusted for centre only, 0.79; 95% CI, 0.53 to 1.18). At six months postnatally the self-reported abstinence was 6.1% in the PA group and 4.1% in the control (odds ratio, adjusted for centre only, 1.55; 95% CI, 0.81 to 2.97).

Psychological outcomes: Between baseline and one week post-quit, the PA group exhibited a significant increase in ratings of confidence for participating in PA relative to the control group ($p=0.005$); however, across this period there was no significant difference in change in ratings for individual cigarette withdrawal symptoms or for urge to smoke or confidence for quitting. There was no evidence for any differences in changes in depression for the two study groups.

Birth outcomes: These were similar between treatment groups; the only significant difference was that more caesarean births occurred in the control group than in the PA group (28.7% vs 21.3%, $p<0.023$).

Maternal weight gain: There was no evidence for any differences in changes in maternal weight gain for the two study groups.

Adverse events (AEs): The rates of AEs and serious adverse events (SAEs) were similar in the two study groups. The number of women or their infants who had at least one AE or SAE was 55.4% in the PA group and 55.7% in the control group

Economic analyses: The total mean costs (costs of delivering interventions plus resource use costs) were £35 per participant lower in the PA group compared with the control group. This was mainly attributable to increased healthcare usage in the control group; however, as shown by the scatterplot, there was substantial uncertainty around this estimate.

Conclusions

Supplementing behavioural support with a PA intervention was no more effective than behavioural support alone in promoting smoking cessation. These findings were observed despite the PA group self-reporting 35-47% greater increases in PA than the control during the intervention period. There was no evidence that the PA intervention increased AEs or had a harmful effect on birth outcomes and there was some evidence that the PA intervention resulted in less caesarean sections. In pregnancy, the physical activity intervention we tested is not recommended for smoking cessation but remains indicated for general health benefits.

Recommendations for research

1. It is not recommended to fund further large scale trials of physical activity for smoking cessation until much less expensive observational studies have been conducted to provide promising leads.
2. Reasons for pregnant smokers' low levels of attendance at supervised PA sessions should be investigated; findings could be used to increase attendance rates.
3. Further methods of increasing PA adherence among pregnant smokers need to be developed and tested.
4. The reasons why few sedentary pregnant smokers were attracted to a PA trial need to be identified and methods are needed to attract these less active pregnant smokers.
5. Studies are needed to establish whether, the previously reported, finding of a short bout of PA reducing cigarette cravings in pregnant smokers is a robust finding
6. There was no evidence of beneficial effects on maternal weight gain or depression. Studies are need which focus on women who are at risk of higher maternal weight gain and which target women who have high levels of depression at baseline.

Implications for health care

There was no evidence that offering regular supervised exercise and PA consultations, in addition to routine smoking cessation support, to women following their first antenatal visit,

is effective for aiding smoking cessation. Therefore, PA is not currently recommended for smoking cessation during pregnancy. In the present study, there was no evidence for the PA intervention moderating cravings/urges to smoke, but it is possible that there are some acute benefits of PA on reducing cravings during pregnancy, and the recommendation to use PA to manage cravings acutely remains for all smokers, including those who are pregnant. The PA intervention did not show any benefit for reducing maternal depression; therefore the intervention cannot presently be recommended for antenatal or postnatal depression in women attempting to quit smoking during pregnancy. There was no evidence for an effect on maternal weight gain, therefore the intervention cannot be currently recommended for moderating this weight gain. There was no evidence of increased adverse events in the PA group and there was some evidence for a reduced incidence of caesarean sections; therefore, in line with current guidance, PA remains indicated for general health benefits in pregnancy, including among pregnant smokers.

Trial registration

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Funding

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Plain English Summary

Smoking during pregnancy damages the growing baby, but stopping smoking before the birth improves infants' health. Giving women regular support to quit is effective, but most women do not quit. In women who are not pregnant, medicines can aid quitting; however, most of these medicines are not allowed in pregnancy or have been found to be unhelpful. In the general population, physical activity reduces urges to smoke, which are the main cause of smoking relapse, and there is mixed evidence that physical activity (PA) programmes can help people quit. We tested whether offering a PA programme helps pregnant women to quit smoking.

Women recorded as smokers, at their first pregnancy-related visit to the health service, were contacted about the study. The 785 women who participated had an equal chance of being offered standard help for stopping smoking given by a health professional, or being offered this help plus a PA programme which encouraged women to incorporate more activity into their days and provided supervised exercise sessions. We compared women's success at quitting at the end of their pregnancy for the two groups. During their pregnancy, women reported how much physical activity they were doing.

Women in the physical activity group reported doing more PA but this did not translate into higher quit rates. The quit rates were low (7.7% in the PA group, 6.6% in the other group), which provides a reminder of the importance of finding improved ways of helping pregnant smokers to stop smoking.

(246 words)

CHAPTER 1: INTRODUCTION

The problem of smoking in pregnancy

Maternal smoking in pregnancy is the main preventable cause of morbidity and death among women and infants. Smoking is associated with adverse pregnancy and birth outcomes, including miscarriage, still birth, prematurity, low birth weight, congenital abnormalities, and neonatal or sudden infant death.[1-3] Smoking also presents immediate risks for the mother, including placental abruption,[4] as well as the longer-term risks reported for smokers in general. Also, the children of mothers who smoke are twice as likely to become smokers.[5] Smoking is pregnancy is a global public health problem. In high-income countries the prevalence of smoking in pregnancy is typically between 10% and 25% and it appears to be reducing.[6-10] However, rates seem to be rapidly increasing in low and middle-income countries.[11] In the UK it is estimated that 12% of women smoke during pregnancy,[7] and as in other high income countries, rates of smoking in pregnancy remain highest amongst younger women and those who are more socially disadvantaged.[7] Smoking cessation during pregnancy improves maternal and birth outcomes,[12] yet only about 25% of pregnant smokers stop for at least part of their pregnancy and around two thirds of these relapse after giving birth.[13]

Treatments to aid smoking cessation in pregnancy

Face-to-face and 'self-help' behavioural support are the only two interventions that have been shown to help pregnant women to stop smoking.[12, 14] Regular sessions of face-to-face behavioural support can increase smoking cessation rates in pregnancy by around 6%,[15] and there is a need to identify other interventions that are effective during pregnancy when combined with this support. The most effective therapy in non-pregnant smokers is a combination of behavioural support plus nicotine replacement therapy (NRT), bupropion, or varenicline.[16-18] However, the efficacy of NRT during pregnancy is not known[19], thus many pregnant women are reluctant to use this,[20] and other smoking-cessation medications are contraindicated during pregnancy.[19] There is a need to identify other non-pharmacological interventions that are effective for smoking cessation during pregnancy.

Evidence for physical activity aiding smoking cessation

Effective pharmaceutical aids for quitting are thought to work mainly through reducing cigarette cravings,[18] and there is good evidence from a meta-analysis to show that physical activity (PA) reduces these cravings,[21] particularly at a moderate or vigorous intensity. Therefore, PA interventions could aid smoking cessation. For non-pregnant smokers, a

Cochrane systematic review has considered the evidence for PA aiding cessation.[22] The majority of the 15 randomized controlled trials (RCTs) reviewed had low statistical power to detect a meaningful difference between the treatment groups, with seven trials having less than 25 participants in each treatment arm. Six adequately powered trials compared a group receiving a PA intervention combined with behavioural support with a group receiving behavioural support alone. Three of these studies showed significantly higher smoking abstinence rates in the PA group versus control group at end of treatment.[23-25] One of these studies also showed that a PA intervention increased abstinence compared with a control group at the 3-month follow-up, and a benefit for exercise of borderline significance (relative risk (RR) = 2.19, p = 0.05) at the 12-month follow-up.[23] A further study showed significantly higher abstinence rates for the exercise group compared with control at the 3-month follow-up, but not at the end of treatment or at the 12-month follow-up.[26] The study with the most intensive PA intervention, entailing thrice weekly sessions of supervised vigorous intensity exercise, showed the strongest effect on abstinence.[23] The other studies involved PA interventions that were relatively less intense, particularly in terms of the extent of supervised exercise, and it is possible that supervised exercise is needed for efficacy. Adequately powered trials are needed with moderate intense exercise, which is likely to be more acceptable than vigorous exercise for most individuals.[27] Physical activity has the potential to aid smoking cessation during pregnancy. Moderate-intensity PA (e.g. brisk walking) is recommended for pregnancy,[28] has been shown to reduce cigarette cravings during pregnancy[29] and pilot work suggests that pregnant smokers are likely to be receptive to a PA intervention.[30]

The effects of physical activity on maternal depression and weight gain

Important secondary outcomes included changes in maternal depression and weight. Antenatal and postnatal depression are important because they are common and are associated with harmful consequences for the mother and child.[31-38] Interventions are needed for preventing and treating these types of depression. Moreover, pregnant smokers are at heightened risk of depression during and after pregnancy and women who quit smoking during pregnancy are more likely to relapse if they experience depressive symptoms.[12,39,40] Thus, it is important that pregnant women who smoke or who are attempting to quit are offered effective interventions for depression. As part of LEAP, we conducted the first trial to assess the effective of a PA intervention on symptoms of antenatal and postnatal depression specifically among smokers.

Excessive gestational weight gain (GWG) is associated with adverse pregnancy outcomes, including large-for-gestational-age-infants and caesarean section.[41,42] In addition, smoking cessation is associated with GWG.[43] Interventions for managing GWG are needed, especially among women attempting to quit smoking, and PA has the potential to help. Observational studies have demonstrated an association between participation in PA and reduced risk of excessive GWG,[44-46] but we are not aware of any large randomised controlled trials which have specificallt examined the effect of a PA intervention on GWG. Among non-pregnant smokers, there is some evidence that PA interventions can limit post-smoking cessation weight gainy.[47] As part of the LEAP trial, we conducted the first large randomised controlled trial to examine the effect of a PA intervention in preventing excessive GWG and postnatal weight retention.

Summary

In summary, smoking in pregnancy is extremely harmful for mother and baby and is an enduring global public health problem. Behavioural support is the only smoking cessation interventions shown to be effective in pregnancy. The evidence for PA programmes aiding smoking cessation is mixed and pregnancy provides a compelling rationale for their use as medication is contraindicated or ineffective. We conducted the **L**ondon **E**xercise **A**nd **P**regnant smokers (LEAP) randomised controlled trial to assess the effectiveness of a PA intervention for smoking cessation during pregnancy.

Main objective

The main objective of the study was to investigate whether standard behavioural support for smoking cessation in pregnancy plus a PA intervention is more effective than behavioural support alone, in achieving biochemically validated smoking cessation, between a quit date and end of pregnancy, for women between 10 and 24 weeks pregnant, who currently smoke one or more cigarettes daily and who smoked at least five cigarettes daily before pregnancy. A further objective was to assess the cost-effectiveness of the intervention for achieving smoking cessation at end of pregnancy.

CHAPTER 2: METHODS

Trial design

LEAP was a multi-centre, pragmatic, randomised controlled, parallel-group trial of a PA intervention. Participants were monitored from their recruitment at between 10 to 24 weeks gestation until end-of-pregnancy, and then followed up by telephone at six months after the birth. The trial protocol has been published[48] and is included as *Appendix 1*.

Participants and Recruitment

Eligibility criteria

Eligible participants were aged 16 to 50 years, 10–24 weeks pregnant (subject to confirmation that they had a scan to show a viable pregnancy), currently smoking at least one cigarette per day, smoking at least five cigarette per day before pregnancy, prepared to quit smoking one week after enrolment, and confirm that they are able to walk continuously for at least 15 minutes. Women were excluded if they are unable to complete self-administered questionnaires in English (because of lack of resources for translators) or if they reported any medical condition that might be exacerbated by exercise. There are no documented contraindications to moderate-intensity exercise, but if the women had been advised by their doctor or midwife not to take exercise during pregnancy, if they had any complications during their pregnancy, or if they had any cautions for taking exercise,[28,49] a consultant obstetrician and gynecologist at their hospital was consulted to check that it was safe for them to participate. Participants joining the trial were monitored at each treatment session for cautions to exercise and for adverse events. Those with drug or alcohol dependence were excluded as the intervention described was not comprehensive enough to address these issues.

Although NRT is licensed for use in pregnancy, there is no evidence for its effectiveness at this time[19] and many pregnant smokers prefer not to use it.[20] Allowing study participants to use NRT might create confounding; therefore, women who indicated that they wished to use NRT on commencing their quit attempt were excluded. Following guidelines,[50] those women who were unable to stop smoking after their quit day, and who expressed a wish to receive NRT, were prescribed NRT by their general practitioner (GP). The participants' GPs, midwives, and obstetricians were be informed of their patient's participation.

Recruiting centres

Participants were recruited from 13 hospital antenatal clinics in England. Initially these were at hospitals in the Greater London area: St George's Healthcare NHS Trust (St George's Hospital), Chelsea and Westminster Hospital NHS Foundation Trust (Chelsea and Westminster Hospital), Guy's and St Thomas'

NHS Foundation Trust (St Thomas's Hospital), Croydon Health Services NHS Trust (Croydon University Hospital, previously known as Mayday Hospital), Imperial College Healthcare NHS Trust (Queen Charlotte's and Chelsea Hospital and St Mary's Hospital), Epsom and St Helier University Hospitals NHS Trust (Epsom Hospital), and Kingston Hospital NHS Trust (Kingston Hospital). Five further sites around England were later added to improve recruitment rates: Surrey and Sussex Healthcare NHS Trust (Crawley Hospital), West Middlesex University Hospital NHS Trust (West Middlesex University Hospital), Mid-Cheshire Hospitals NHS Foundation Trust (Leighton Hospital), King's College Hospital NHS Foundation Trust (King's College Hospital), and Medway Foundation Trust (Medway Maritime Hospital).

Researchers

At each centre a dedicated research midwife, research nurse or research psychologist undertook all trial related procedures, including delivering all the interventions and administering all the outcome measures. Researchers were trained by the chief investigator/trial manager (Professor Ussher) in research procedures, including screening, enrollment and consent procedures. They also attended certified Good Clinical Practice training. Researchers were trained to national standards to provide behavioural support for smoking cessation and physical activity.[51]

Recruitment and consent

Smoking status for all pregnant women was routinely recorded in the hospital computerized patient administration system (PAS) at the first antenatal booking visit, which is typically at 9–14 weeks of gestation. At this time, the hospital midwife informed all women recorded as smokers that it is the hospital's policy to telephone them to offer smoking-cessation support. This support would usually be offered by their local NHS Stop Smoking service (SSS), but during the period of recruitment to the study a trial researcher telephoned the women. Those who were interested in receiving help with quitting were invited to join the trial or were offered referral to the PCT, as per usual practice. Those women expressing interest in volunteering were screened for eligibility by the researcher via telephone (*See Appendix 2 – Screening sheet*), and eligible women were sent a patient information sheet (PIS). The following methods of recruitment were used:

- On recording women as smokers, hospital midwives routinely passed referral forms to the researcher. In some cases, these referral forms would be available before the smoking status of the women was recorded in the PAS and in these cases the researcher extracted the woman's contact details from the referral form rather than from the PAS and telephoned women.
- In cases where the woman's smoking status appeared in the PAS, before a midwife referral form was received, the researcher extracted the woman's contact details from the PAS and telephoned her.

- A flyer containing brief information about the trial was included in all the women's pack for their first antenatal booking appointment and the women were invited to call the researcher if they were interested in finding out more about the study.
- Women who had seen posters advertising the study in hospitals or children's centres could contact the researchers directly.
- We had initially planned to distribute a questionnaire at the first ultrasound visit inviting women to take part. This approach was piloted at several sites in the first month of the study and it had a low response rate and was labour intensive and therefore was abandoned.

After having the chance to consider the PIS for at least 24 hours, and to discuss the study with the researcher, women who volunteered were offered an appointment at a community-based children's centre or at their local hospital. At the first appointment they gave their written informed consent before trial data were collected. In addition to trial participation, women were asked to give consent for researchers to have access to their and their child's medical records, for information held by the NHS to be used to keep in touch with them and to follow their health status and for the researcher to inform their GP, midwife and obstetrician about their participation in the study.

Interventions

The interventions followed CONSORT guidelines for non-pharmacologic interventions.[52,53] Delivery of the interventions was standardized by training and by the therapists following manuals (*see Appendix 3 - Smoking Cessation Manual and Appendix 4 - Physical Activity Manual*). The initial competence of the therapists was assessed by the Trial Manager/chief investigator by observing role-play scenarios during training. The fidelity of the interventions were monitored during the first six months by regular observations (at least five intervention sessions) by the trial manager/chief investigator. All sessions were face-to-face and one-to-one, and were delivered in a private room at the hospital or in a community Health/children's centre. Social cognitive (learning) theory[54] was the theoretical basis for the interventions. This theory recognizes the interplay of individual factors (for example, self-efficacy to quit smoking or increase PA) and social/environmental factors (for example, social support) on health behavior change. For each session that they attended, the women were paid £7 for their travel expenses.

Control group (standard behavioural support for smoking cessation)

Those in the control group received behavioural support for smoking cessation, which is generally provided via the NHS SSS to pregnant women as part of 'usual care'. By extracting the elements of the intervention from written manuals and materials provided by the programme (*see Appendix 3 – Smoking cessation manual*), the contents of the intervention were classified in accordance with the taxonomy of behavior-change techniques (BCTs) described by Michie and colleagues, and used in individual

behavioural support for smoking cessation (*see Table 1*).[55] Participants were offered six weekly sessions of 20 minutes of behavioural support for smoking cessation, commencing one week before the quit date and ending four weeks afterwards. The intervention (*see Table 1*) incorporated all 43 BCTs for smoking cessation defined by Michie and colleagues,[55] except for the BCT 'provide rewards contingent on successfully stopping smoking', although financial rewards were offered to increase compliance (*see Table 2*). Continuing support was offered to women who failed to quit or relapsed to smoking.

Treatment group

In addition to behavioural support for smoking cessation, those in the PA group received a PA intervention, combining PA consultations and supervised exercise. By extracting the elements of the PA consultation from written manuals and materials provided by the PA programme (*see Table 3*), the contents of the PA consultation have been classified in accordance with the taxonomy by Michie and colleagues of behavioural change techniques used to help people change their PA behaviors.[56] There were 14 sessions of supervised exercise, twice a week for 6 weeks (one session with behavioural support for smoking cessation), and then weekly for 2 weeks. Following a familiarization session at the first visit, participants were advised to aim for 30 minutes of continuous treadmill walking during each session. Following guidelines,[57] moderate-intensity exercise was prescribed according to age and current activity levels, and monitored using a polar heart-rate monitor. Intensity of exercise was also guided by a rating of perceived exertion (RPE)[58] ('fairly light' to 'somewhat hard') and by the 'talk test', which indicates that the intensity of activity is too high if the woman cannot hold a conversation.

Twice in the first week, and then weekly (alternating with behavioural support for smoking cessation), women were offered a 20 minute PA consultation (total of 9 sessions), towards increasing their additional 'home-based' PA. This took place before the treadmill walking and the researcher worked through a booklet with the participant (*see Appendix 5*), which the participant retained. The intervention (*see Table 3*) incorporates 19 of 40 BCTs for increasing PA as defined by Michie and colleagues.[56] The participants were encouraged to view PA as a self-control strategy for reducing cigarette cravings and withdrawal,[59] and to maintain any increases in PA after their pregnancy. Following recommendations for pregnancy,[28,60] the women were advised to be active for continuous periods of at least 10 minutes at a time, progressing towards accumulating 30 minutes of activity on at least 5 days of the week. The emphasis was on brisk walking, which is popular among pregnant smokers.[61] As a further option, a home-based antenatal exercise DVD and booklet were provided. In addition, participants were given a pedometer for monitoring their daily steps (Digi-Walker SW-200; Great Performance Ltd, London, UK). Pedometers have been shown to increase activity levels in women,[62] and are acceptable during pregnancy[63] and among pregnant smokers.[30] Participants were asked to log their daily steps, with the researcher calculating a 10% increment every two weeks, gradually progressing towards 10,000 steps a day.[64]

Table 1. Behavior change techniques (BCTs) used in the smoking-cessation consultations

Week	Session number	Session content	BCTs used (Michie categories[a])
1	Session 1 (1 week before quit day)	Explain the treatment, including timing of quit	RC4, BS4
		Measure expired CO and explain purpose	RC3
		Assess and discuss current and past smoking behavior	RI1
		Identify reasons for wanting and not wanting to quit	BM9
		Assess current motivation/confidence for quitting	R12
		Discuss past attempts at quitting	R13
		Prepare for the quit attempt	BM6, BS3
		Discuss use of social support	A2
		Advise on reducing smoking cues	BS8
		Advise subject to note the times when they are likely to lapse	BS6
		Facilitate relapse prevention planning and coping	BS2
		Identify barriers to quitting and address these barriers	BS1
		Emphasize choice (for example, when the participants take their final smoke)	RD2
		Provide information about the consequences of smoking during pregnancy	BM1, RC5
		Explain about quitting abruptly, rather than cutting down	BM10
		For all sessions:	

		Allow time for questions	RC2
		Summarize	RC9
		Use reflective listening	RC7
		Elicit participant's views	RC8
		Build a general rapport	RC1
		Give praise for progress	BM7
		Tailor the interactions	RD1
2	Session 2 (quit day)	Look for reasons why the woman is a good prospect	BM2, BM3
		Explain about cigarette withdrawal symptoms and strategies for dealing with them	RC6
		Identify barriers to quitting and address these barriers	BS1
		Advise on avoiding social cues for smoking	BS11
		Advise on changing routine	BS7
		Advise on conserving mental resources	BS10
		Set graded tasks (for example, take 1 hour/day at a time)	BS9
3	Session 3 (1 week after quit day)	Check smoking status	BS5
		Assess withdrawal symptoms	R14
		Reassure about the norms for these symptoms	RC10, BM5
		Advise subject to monitor when they want to smoke	BS6
		Assess CO and give feedback about whether reading has reduced	BM11, BM3

		Discuss planning and coping strategies to prevent relapse	BS2
		If they, have relapsed ask them to commit to a new quit date	BM6
		Advise about use of NRT	A1
		Liaise with PCT about obtaining NRT	A3
		Encourage subject to see themselves as a non-smoker	BM8
		Remind them of lottery prize for attending all sessions	BM7
4	Session 4 (2 weeks after quit day) onwards	Assess CO	BM11
		Check smoking status	BS5
		If they are struggling offer further support from PCT	A5
		Discuss relapse prevention planning and coping strategies for after birth	BS2, BM8
		Emphasize importance of not having a single puff	BM6
		If subject has relapsed, set a new quit date, and review use of NRT	A4

CO, carbon monoxide; PCT, primary care trust; NRT, nicotine replacement therapy.

[a]Michie categories are defined as follows.

Specific focus on the target behavior (B) and maximizing motivation (M). BM1: provide information on consequences of smoking and smoking cessation. BM2: boost motivation and self-efficacy. BM3: Provide feedback on current behavior. BM5: provide normative information about others' behavior and experiences: BM6: prompt commitment from the client there and then. BM7: Provide rewards contingent

on effort or progress. BM8: strengthen ex-smoker identity. BM9: identify reasons for wanting and not wanting to stop smoking. BM10: explain the importance of abrupt cessation. BM11: measure CO levels.

Maximizing self-regulatory capacity and skill (BS). BS1: facilitate barrier identification and problem-solving. BS2: facilitate relapse-prevention and coping. BS3: facilitate action-planning/develop treatment plan. BS4: facilitate goal-setting. BS5: prompt review of goals. BS6: prompt self-recording. BS7: advise on changing routine. BS8: advise on environmental restructuring. BS9: set graded tasks. BS10: advise on conserving mental resources. BS11: advise on avoiding social cues for smoking.

Promoting adjuvant activities (A). A1: advise on stop-smoking medication. A2: advise on/facilitate use of social support. A3: adopt appropriate local procedures to enable clients to obtain free medication. A4: ask about experiences of stop-smoking medication that the smoker is using. A5: give options for additional and later support.

General aspects of interaction focusing on delivery of the intervention (RD). RD1: tailor interactions appropriately. RD2: emphasize choice.

General aspects of interaction focusing on information gathering (RI). RI1: assess current and past smoking behavior. RI2: assess current readiness and ability to quit. RI3: assess history of quit attempts. RI4: assess withdrawal symptoms.

General aspects of interaction focusing on general communication (RC). RC1: build general rapport. RC2: elicit and answer questions. RC3: explain the purpose of CO monitoring. RC4: explain expectations regarding treatment programme: RC5: offer/direct toward appropriate written materials. RC6: provide information on withdrawal symptoms. RC7: use reflective listening. RC8: elicit client views. RC9: summarize information/confirm client decisions. RC10: provide reassurance.

Table 2. Financial incentives offered to trial participants

Incentive occasion	Maximum financial incentive, GBP	
	Exercise group	**Control group**
Annual lottery with three prizes of £100[a] for attending at least 80% of treatment sessions	100	100
£7[b] travel expenses for each session attended	98 (14 sessions)	42 (6 sessions)
£10[a] for follow-up at end of pregnancy	10	10
£10[a] for follow-up at 6 months after birth	10	10
£25[a] if ≥ 5 days of accelerometer data recorded	25	NA
Total	£243	£162

NA, not applicable

[a]Shopping vouchers, [b]cash.

Table 3. Behavior change techniques (BCTs) used in the physical activity (PA) consultations

Week	Session number	Session content	BCTs used (Michie categories[a])
1	Session 1 (one week before quit day)	Review current PA and discuss PA benefits	1, 2
		Explain and demonstrate use of treadmill and pedometer	7, 21, 22, 26
		Check PA confidence levels using scaling questions	16
		All sessions:	
		Agree PA goals	10
		Provide weekly PA and step-count diaries	16
		Allow time for questions, summarize, use reflective listening, elicit participant's views, build a general rapport	
		Give praise for effort and for achieving PA goals	12, 13
1	Session 2	Review PA goals and effect of PA on cravings	7, 9, 10
		Complete cost-benefit analysis for increasing PA	2
		Identify PA barriers and problem solve	8
		Explain and demonstrate exercises in booklet	21, 22, 26
		Provide information on places to exercise	20
		Discuss time management and exercise habits	23, 38
		Plan social support	29
		Provide weekly PA diary and step-count diary	16
2	Session 3 (quit day)	Review PA goals, set heart-rate targets on treadmill	10

		Identify PA barriers and problem solve	8
		Provide weekly PA diary and step-count diary	16
		Check PA confidence levels with scaling questions	8
3	Session 4(one week after quit day) onwards	Review PA goals, set heart-rate targets on treadmill	10
		Plan for relapse prevention/coping	35
		Review exercises in booklet	21, 22, 26
		Review social support	29
		Use imagery to encourage identity as an 'exerciser'	34
		Provide weekly PA diary and step-count diary	16
		Reminder that sessions reduce to once a week for the last 2 weeks of the programme	27
		Check PA confidence levels with scaling questions	8

[a]Michie categories are defined as follows.

1) Provide information on consequences of behavior in general. 2) Provide information on consequences of behavior to the individual. 7) Action-planning. 8) Barrier identification/problem-solving. 9) Set graded tasks. 10) Prompt review of behavioural goals. 12) Prompt rewards contingent on effort or progress towards behavior. 13) Provide rewards contingent on successful behavior. 16) Prompt self-monitoring of behavior. 20) Provide information on where and when to perform the behavior. 21) Provide instruction on how to perform the behavior. 22) Model/demonstrate the behavior. 23) Teach subject to use prompts/cues. 26) Prompt practice. 27) Use of follow-up prompts. 29) Plan social support/social change. 34) Prompt use of imagery. 35) Relapse-prevention/coping planning. 38) Time management.

Randomisation and blinding

An independent statistician generated a randomisation list using Stata, with random permuted blocks of random size stratified by recruitment centre. At enrollment, the sequence was concealed from researchers who had to confirm consent and eligibility on an online database before allocation was revealed. The online database was created by the Nottingham University Clinical Trials Unit (CTU) and held on a secure server in accordance with their standard operating procedures (SOP). Allocation was concealed from the participant until they had completed all baseline assessments. The sequence of treatment allocations was concealed until interventions had all been assigned and recruitment, data collection, and laboratory analyses were complete.

Data collection

At baseline, researchers recorded demographic characteristics, (including age, marital status, number of children, highest educational qualification, ethnicity, occupation, weeks of gestation, and history of premature births) and smoking characteristics (including cigarettes smoked per day (now and before pregnancy), weekly urge to smoke (combining ratings of strength and frequency of urges),[65,66] cigarette withdrawal symptoms,[65,66] and Fagerström Test for Cigarette Dependence score,[67,68] as well as the partner's smoking status). Depression was assessed with the 10-item Edinburgh Postnatal Depression Scale (EPDS).[69] Physical activity levels in the previous week (bouts of $\geq$10 minutes) were assessed for both groups using the 7-day Physical Activity Interview.[70] The woman's confidence about taking up regular PA[71] and stopping smoking[72] was also recorded. The questionnaire showing assessments at baseline, including assessments repeated at further time points, is included as *Appendix 6*. The timing of data collection at further measurement times is given in the outcomes section below.

Recording of adverse events

During all contacts, participants were asked about adverse events. Medical records were examined monthly for adverse events, by research midwives, and were examined after delivery for maternal and infant outcome data. Researchers then summarised the descriptions in the case report forms and on the online study database. Descriptions were used to code the adverse events according to standard terms in the Medical Dictionary for Regulatory Activities. Fetal deaths were recorded including: miscarriage (non-live birth prior to 24 weeks gestation), stillbirth (non-live birth at 24 weeks gestation or later) and neonatal death (i.e. from live birth to 28 days).

Outcome measures

Timing of outcome measures

During the intervention period, the main assessment points were at one week, four weeks and six weeks after the quit day. The assessment at one week was in order to assess the early impact of the intervention, when the vast majority of the sample was retained, on outcomes for cigarette withdrawal symptoms, urges to smoke, confidence for quitting and taking PA, reports of PA. The outcome as four weeks is a standard time for measuring short-term abstinence and is when the NHS stop smoking services assess abstinence. The 6 week assessment was timed to coincide with the end of the stop smoking programme. There were follow-ups at end of pregnancy and six months after the birth.

Primary outcome to end of pregnancy

The primary outcome was self-reported, continuous abstinence from smoking between the quit date and end of pregnancy, validated by exhaled carbon monoxide (CO) (Smokerlyzer; Bedfont Scientific Ltd, Maidstone, Kent, UK) or salivary cotinine (Salimetrics Europe Ltd, Newmarket, UK). Expired CO levels were assessed weekly up to 4 weeks after the quit day and at end of pregnancy. Saliva cotinine levels were measured at 4 weeks after the quit day and at the end of pregnancy, only among those who self-reported having smoked less than 5 cigarettes in total (on up to five occasions) since the quit day.

The primary outcome was operationalised as follows:

Continuous abstinence was defined as having smoked less than 5 cigarettes in total (on up to five occasions) since the quit day.[73]

Exhaled CO: The criteria for confirming abstinence was a reading of <8ppm.[74]

CO was assessed weekly up to four weeks after the quit day and at end of pregnancy.

Salivary cotinine: The criteria for confirming abstinence was a value of <10ng/ml.[75]

Cotinine was measured at four weeks post quit-day and at end of pregnancy.

End of pregnancy: The aim was follow-up the woman within two weeks of the birth; however, it was acceptable for the primary outcome to be taken at any time between 36 weeks gestation and 10 weeks after the birth.

The primary outcome was dichotomous; i.e. abstinent or non-abstinent.

For a participant to be classed as abstinent from smoking at end of pregnancy (i.e. positive primary outcome)**:**

<u>At 4 weeks post-quit (It was acceptable for this measure to be taken between 25 days to 6 weeks post-quit):</u>

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' or 'missing' (i.e. any response other than 'yes, more than 5 cigarettes')

AND CO is <8ppm

AND/OR cotinine is <10ng/ml

OR CO or cotinine is missing

AND

<u>At end of pregnancy</u>:

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' (i.e. any response other than '5 or more cigarettes')

AND CO is <8ppm

AND/OR cotinine is <10ng/ml

- Concentration of either exhaled CO or salivary cotinine was used to validate abstinence; if both measures were available both were required.
- Some women will not have data for self-report of smoking or biochemical validation at 4 weeks. If these women are confirmed as abstinent at end of pregnancy it will be considered as a positive primary outcome.

For a participant to be considered as non-abstinent from smoking at end of pregnancy (i.e. negative primary outcome)**:**

At 4 weeks or end of pregnancy:

- Have you smoked at all since your quit day?= 'yes, more than 5 cigarettes'
- CO or salivary cotinine values do not confirm abstinence.
- Has withdrawn from the study (i.e. refuses follow-up).
- Fails to set a quit date which the follow-up assessment can be referenced against.

At end of pregnancy:

- Refuses to allow biochemical validation
- Refuses to self-report number of cigarettes smoked.
- Unable to contact in order to confirm smoking status (i.e. lost to follow-up).

Secondary outcomes

Biochemically validated continuous smoking abstinence was also assessed at four weeks after the quit day and six months after the birth. In addition, we assessed biochemically validated continuous smoking abstinence with a stricter criteria whereby no cigarettes are allowed after the quit day, at four weeks after the quit date, at the end of pregnancy and at six months

postnatal. Self-reports of smoking status at six months after the birth were reported via telephone and were not biochemically validated. Many women report that, rather than stopping smoking, they reduce their smoking during pregnancy,[76,77] and there is some evidence to suggest that a reduction in smoking of 50% or more is associated with increased infant birth weight.[78] Therefore, levels of smoking reduction were assessed for those women who relapse.

Other secondary outcome measures were: changes in urge to smoke, tobacco withdrawal symptoms, and confidence in stopping smoking and in maintaining regular PA between baseline and one week after the quit day. We also assessed changes in depression between baseline, end of pregnancy and 6 months after the birth, as well as changes in maternal weight between baseline, 4 weeks after the quit date, and end of pregnancy. Further self-reports of PA levels were collected at weeks 1, 4, and 6 after the quit date and at both follow-ups (i.e. end of pregnancy and 6 months after birth). To validate self-reported PA, a 10% random subsample of participants had PA objectively measured via an accelerometer (Model GT1M or GT3X; Actigraph, Pensacola, FL, USA). During the fourth week after the quit date, the accelerometer was worn over the right hip, for seven consecutive days, recording non-water based activities during waking hours at one minute epochs. The Actigraph has been shown to be practicable and valid during pregnancy.[79-81] Duration of treadmill exercise and attendance rates were recorded. Use of NRT was monitored throughout the intervention period. At the end of pregnancy follow-up participants were asked if they had received any face-to-face support to stop smoking during your pregnancy, beyond that provided in the study.

The following birth and maternal outcomes were extracted from participant's hospital records:

1. Birth weight
2. Gestational age at delivery
3. Preterm birth (<37 weeks gestation)
4. Apgar score
5. Cord blood pH
6. Neonatal intensive care unit (NICU) admission
7. Elective termination
8. Maternal mortality
9. Mode of delivery

Statistical methods

The Statistical Analysis Plan (SAP), which is presented in *Appendix 7*, was finalised before any analyses started. The analysis for the primary outcome was conducted by an independent statistician with allocation to the two study groups concealed until the analysis was completed. Analyses were performed using Stata version 11.2 (StataCorp LP, TX, USA) and SPSS version 19 (IBM, UK). Throughout, a p value of <0.05 was taken to indicate statistical significance, and 95% confidence intervals were calculated.

Sample size

We anticipated a cessation rate of 15% in the control group, on the basis that 9% of pregnant women who are smokers stop smoking with usual care after their first antenatal visit, and that with behavioural support another 6 to 7% quit.[15] Based on pilot work,[30] a cessation rate of 23% was projected in the treatment group. We calculated that 866 participants would provide 83% power at a 5% significance level to detect an absolute difference of eight percentage points in the rate of the primary outcome between the two groups, corresponding to an odds ratio of 1.69.

Analysis for the primary outcome at end of pregnancy

Analysis was on an intention-to-treat basis; participants with missing outcome data were assumed to be smoking.[73] The proportion of women reporting continuous smoking abstinence at end of pregnancy was compared between study groups using logistic regression, with adjustment for recruitment centre. Statistical significance was assessed with the likelihood-ratio test, with the estimate of effect given as the odds ratio (OR) and 95% confidence interval (CI). A secondary analysis adjusted for centre, nicotine dependence, age, depression, maternal educational level, and partner's smoking status, as potentially important prognostic baseline factors.[82] In addition, as it was observed that the vast majority of participants reported high levels of PA at baseline, we tested for an interaction between baseline PA (<150 minutes/week MVPA versus $\geq$ 150 minutes/week MVPA) and the treatment effect for the primary outcome. Exclusively in the PA group, we also assessed, among those reporting <150 minutes/week MVPA at baseline, whether reporting $\geq$ 150 minutes/week MVPA at four weeks or six weeks after the quit day was associated with smoking abstinence at those times. For the primary outcome, to assess the influence of the assumption that missing data equals 'smoking' on the effect size, we used the Hedeker method to test various scenarios of the association between smoking and having missing data.[83] Other outcomes for smoking cessation were analysed in a similar way.

Analysis for secondary outcomes

For ratings of withdrawal symptoms, urge to smoke, confidence for quitting smoking and confidence for taking PA we calculated a change score between baseline and one week post-quit and used t-tests to compare the score for the two groups. We compared the use of NRT and behavioural support between the two groups using chi-squared tests.

Physical activity outcomes

Self-reported weekly minutes of MVPA were log transformed (log base 10) to normality, and the difference in self-reported PA between the groups over time was analysed using a mixed effects model to account for within person correlations over time. The accelerometer data were analysed using KineSoft software (Version 3.3.76; Loughborough, UK). Files with at least 10 hours of valid wear time on one or more days were retained in the analyses. Standard cut-points were used to determine MVPA.[84] Consistent with the self-report data, only MVPA sustained for at least 10 minutes was included in the assessment of validity via correlational analysis. The validity of the self-reports was also assessed by examining the difference between the self-report and accelerometer data using a Bland-Altman plot.[85] Accelerometer measured MVPA was compared between the groups use a Mann-Whitney test.

Fetal and maternal birth outcomes

Fetal and maternal birth outcomes were compared for binary outcomes using logistic regression adjusted for recruitment centre. For continuous outcomes we compared study group means using multiple linear regression, again with adjustment for recruitment centre. For fetal outcomes, the primary analysis was of singleton births. We also conducted a sensitivity analysis, including multiple births, with clustering of outcomes accounted for using an approach previously published. This adapts methodology previously created for use with cluster randomised RCTs, assuming that each woman is regarded as the 'cluster' and her number of offspring the cluster size.[86] A chi-squared test was used to compare the total number of women or their infants who had at least one AE or SAE.

Depression outcome

One participant was randomised but withdrew consent, without reason, before providing any data. Thus, 784 women comprised the sample for the depression analysis. All 784 participants provided EPDS scale data at baseline, 383 (48.9%) and 268 (34.2%), respectively, provided this data at follow-up at the end of pregnancy and six-months postnatally. First, we checked whether those with EPDS data at the two follow-ups (end of pregnancy, six months postnatally) had similar baseline characteristics, and quit rates at end of pregnancy, and amount of physical activity reported, as those from the total trial sample,

Then, we examined whether the baseline characteristics of the PA and control groups were similar in the sub-samples with EPDS data at the two follow-ups.

In order to maximise statistical power, the EPDS data were treated as a continuous variable. We used a mixed-effect linear model with bootstrap validation, adjusted for baseline EPDS score, and presented the estimated difference in score at end of pregnancy and at six months follow-up, for the PA group versus control group. This model accounts for within person correlation over time and assumes that data is missing at random for the participants with missing EPDS data at follow-ups. In a final linear mixed effect model, analysis was further adjusted for the following potential predictors of postnatal depression: marital status, age at leaving full time education (as a proxy for socioeconomic status), body mass index (BMI) and young age (i.e., age $\leq$ 20 years). At end of pregnancy, as some of the women provided EPDS data before the birth and some after the birth, we used t-tests to explore whether EPDS scores were similar at these two times.

Maternal weight outcome

First, we compared the sub-sample providing maternal weight at end of pregnancy (n=263) with the main LEAP Trial sample (n=785) for baseline characteristics, and for key end of pregnancy outcomes which might be associated with weight gain (i.e. quit rates, PA levels, and depression scores). As we are conducting separate analysis for those providing end of pregnancy weight before the birth (gestational weight gain) and after birth (postnatal weight retention), we did this separately for the subsamples before and after birth. Secondly, in the combined sample at end of pregnancy, and in the sub-samples before and after delivery, we compared baseline characteristics between the two randomisation groups. Subsequent analysis adjusted for any baseline differences between groups, for variables that might affect weight.

For all analyses, the main outcome was the mean change in maternal weight (kg) (i.e. weight in early pregnancy minus weight at end of pregnancy), computed separately for the sub-samples before and after the birth. Weight change was compared between the two randomization groups using linear regression analyses. All the regression analyses were then adjusted for the following potential prognostic factors in weight change during pregnancy: age, number of previous pregnancies and weight at early pregnancy. As a sensitivity analysis, we further adjusted the results for baby's weight, which is important because women who quit may have bigger babies than those who do not quit, and continuous rates of smoking abstinence at end of pregnancy. For the subsamples before and after birth, the latter analyses

were limited to samples of n=133 and n=120 respectively due to missing data in baby's weight and excluding three sets of twins.

For the sub-sample with gestational weight gain (i.e. weight measured before birth) it is important to consider that women will have delivered at different weeks of pregnancy; therefore, besides using the change in the crude measure of weight, we computed the change in the mean kg per gestation week. This was calculated by dividing the total weight gain by the actual number of weeks of pregnancy. The regression models used for crude weight change were then repeated using weight change adjusted for gestation weeks as the dependent variable. In order to assess if weight change is modified by whether the women were obese at baseline we also added an interaction between the effect of PA and whether the individual was obese at baseline. Weight at early pregnancy was not added to this model due its co-linearity with obese versus non-obese

Next, using Institute of Medicine (IOM) guidance,[87] we investigated what proportion of women gained excessive gestation weight (coded 'yes' or 'no') relative to their early pregnancy BMI. A woman was considered to have gained excessive gestation weight if either she was underweight according her early pregnancy BMI and her gestational weight gain was more than 18 kg, or her weight was healthy and her gestational weight gain was more than 16 kg, or she was overweight and her gestational weight gain was more than 11.5 kg, or she was obese and her gestational weight gain was more than 9 kg. We used logistic regression analyses to compute odds ratios of excessive gestational weight gain for each BMI category and for the randomized groups. In the final logistic regression model, the results were adjusted for all prognostic factors that were used in the above main analyses, except weight at early pregnancy.

Trial management

The trial was co-ordinated from a central trial office located within St George's University of London, with the day-to-day running supervised and organised by the Trial Manager and Administrator. The trial was sponsored by St George's University of London (SGUL) and conducted in accordance with Good Clinical Practice (GCP) guidelines. The CI/trial manager and trial administrator received GCP training. Monthly research staff meetings were held at SGUL.

Nottingham Clinical Trials Unit (NCTU) provided a web-based database and randomisation system and data management reports. The system was held on a secure server in the NCTU, had a full electronic audit trail and full back-ups of the database were made every 24 hours. All the outcome data was entered directly into the online forms by the

participants or researchers. The database included validation checks whereby responses not meeting expected criteria would be flagged so that data entry errors were minimised.
An independent Trial Steering Committee met once or twice a year to monitor the conduct and progress of the trial and to address any safety issues. London-Wandsworth Research Committee granted national research ethical approval, with additional local approvals for each recruitment centre. The NHS National Institute for Health Research (NIHR) Primary Care Research Network (PCRN) adopted the study. For Public and Patient Involvement (PPI) in the study *see Appendix 10*.

The protocol[48] was published (*see Appendix 1*) and included a description of approved amendments made to the original protocol after the start of recruitment; details of these amendments are given below:

Protocol amendments

1) For the follow-up at end of pregnancy, the valid period for assessment was originally defined as 38 weeks gestation to two weeks after the birth. As there were a number of women who could not be contacted to be followed up during this time frame, the valid period was extended to 36 weeks gestation to 4 weeks after the birth (approved by the research ethics committee on 18 May 2010). However, because there were still some women being followed up later than four weeks after the birth, the valid period was further revised to 36 weeks gestation to 10 weeks after the birth (approved 31 Jan 2012). The aim remained to attempt to follow-up as many women as possible within two weeks of the birth.

2) To give the women an incentive to complete the follow-ups at end of pregnancy and six months after the birth, all women who complete these follow-ups were given a £10 shopping voucher for each of the follow-up sessions attended (approved 18 May 2010).

3) Originally, to be eligible women had to report smoking at least 10 cigarettes a day before their pregnancy. We found that a good number of women reported smoking five to nine cigarettes a day at this time. Therefore, we extended the eligibility criteria to include women smoking at least five cigarettes a day before pregnancy (approved 15 September 2010). These women are still likely to be dependent on smoking, as there is evidence that women who say they were smoking five to nine cigarettes before pregnancy are back to smoking 14 cigarettes a day at 18 months postnatally.[88]

4) Initially, women had to be between 12 and 24 weeks' gestation to be eligible for the trial. However, since the trial began, most of the hospital trusts began offering earlier antenatal

booking appointments (before 12 weeks gestation), and because we wished to recruit the women as early as possible in pregnancy, we revised this to 10 to 24 weeks gestation (approved 31 Jan 2012).

5) This amendment was approved after publication of the protocol: 'Partners smoking status' was adjusted for in the final model for all the outcomes related to smoking abstinence.

Trial extension

The NIHR-HTA agreed a 12 month time extension. This was necessary as the rate of recruitment had been slower than anticipated and several additional recruitment sites had been established. Through careful budgeting, mostly due to the researchers working less hours and the CI taking the role of Trial Manager, the majority of this extension was funded within the original budget. An addition to the budget was awarded to extend the contract of the trial administrator.

CHAPTER 3: RESULTS

Recruitment of participants

Recruitment took place between April 2009 and November 2012. Follow-up, at six months after the birth, continued until January 2014. Figure 1. shows accrual for the original recruitment target of N=866 participants, the revised target of N=774 (agreed with NIHR-HTA following approval of trial extension) participants and the actual N=789 participants who were randomised. Four women were excluded post-randomization; two women (PA group) were enrolled twice in sequential pregnancies and their second enrolment was removed. The other two women (control group) were excluded because they were found to be ineligible at their baseline visit before any data was collected, and had been randomised erroneously. When ineligible participants are mistakenly randomised into a trial it is acceptable, within an intention-to-treat approach, to exclude participant's data, without risking bias.[89] Table 4 shows the recruitment numbers for each centre for the final sample size of 785 participants included in the analysis. As shown in Table 5 over two thirds of participants were recruited via midwife referral and over a quarter via direct calling, through extracting contact information from the PAS. Less than 4% were recruiting using the other methods combined.

The CONSORT diagram (*see Figure 2*) shows the flow of participants through the study to the primary endpoint at end of pregnancy. Around 8,100 women were recorded as smokers in the PAS. Of these, approximately a quarter we were unable to contact, just over a quarter said that they were not interested in participating and a little less than a third did not meet the inclusion criteria. A breakdown of the reasons for excluding participants is presented in Table 6. The main reason for exclusion was the women smoking less than one cigarette a day. Overall, of the 8096 women recorded as smokers at their first antenatal visit, 9.7% (785) were included in the ITT analysis. Of 785 pregnancies, 774 were singleton, 10 were twins and one was unknown as she withdrew consent.

Baseline characteristics

Participants in the two groups had similar baseline characteristics (*see Table 7*). Women were recruited to the trial at a mean gestational age of 16 weeks and on average they were 27 years of age. Over half (53.6%) were smoking at least 10 cigarettes a day. By self-report, 70% were achieving the recommendation of 150 minutes a week of MVPA.[27,28]

Follow-up rates

At four weeks after the quit day, 316 (80.6%) were successfully followed up in the PA group and 319 (81.2%) in the control group. At the end of pregnancy follow-up, 587 (74.8%) women were assessed before the birth and 198 (25.2%) were assessed after the birth. The overall follow-up rate

for the primary outcome at end of pregnancy (*see Figure 2*) was 88.8% (697 participants), and there was no evidence of a significant difference in the follow-up rate between study groups. Of the 88 participants (11.2%) who did not complete the assessments necessary for the analysis of the primary outcome, 43 (48.9%) were known to have smoked from the follow-up assessments (PA group: n=19, control: n=24). Also, of the remaining 45 participants (5.7% of total), 24 had a fetal or infant death and were not asked about smoking status, plus one individual withdrew consent and all were assumed to be smoking at the end of pregnancy.

Rates of biochemical validation of smoking status

For the majority of participants who reported that they were not smoking biochemical validation was obtained. At end of pregnancy, validation rates for smoking status were 71.4% (30/42) in the PA group and 56.8% (25/44) in the control group (p=0.158); at four weeks, the rates were 98.0% (50/51) and 100.0% (61/61) (p=0.272), respectively.

Figure 1. Cumulative trial recruitment

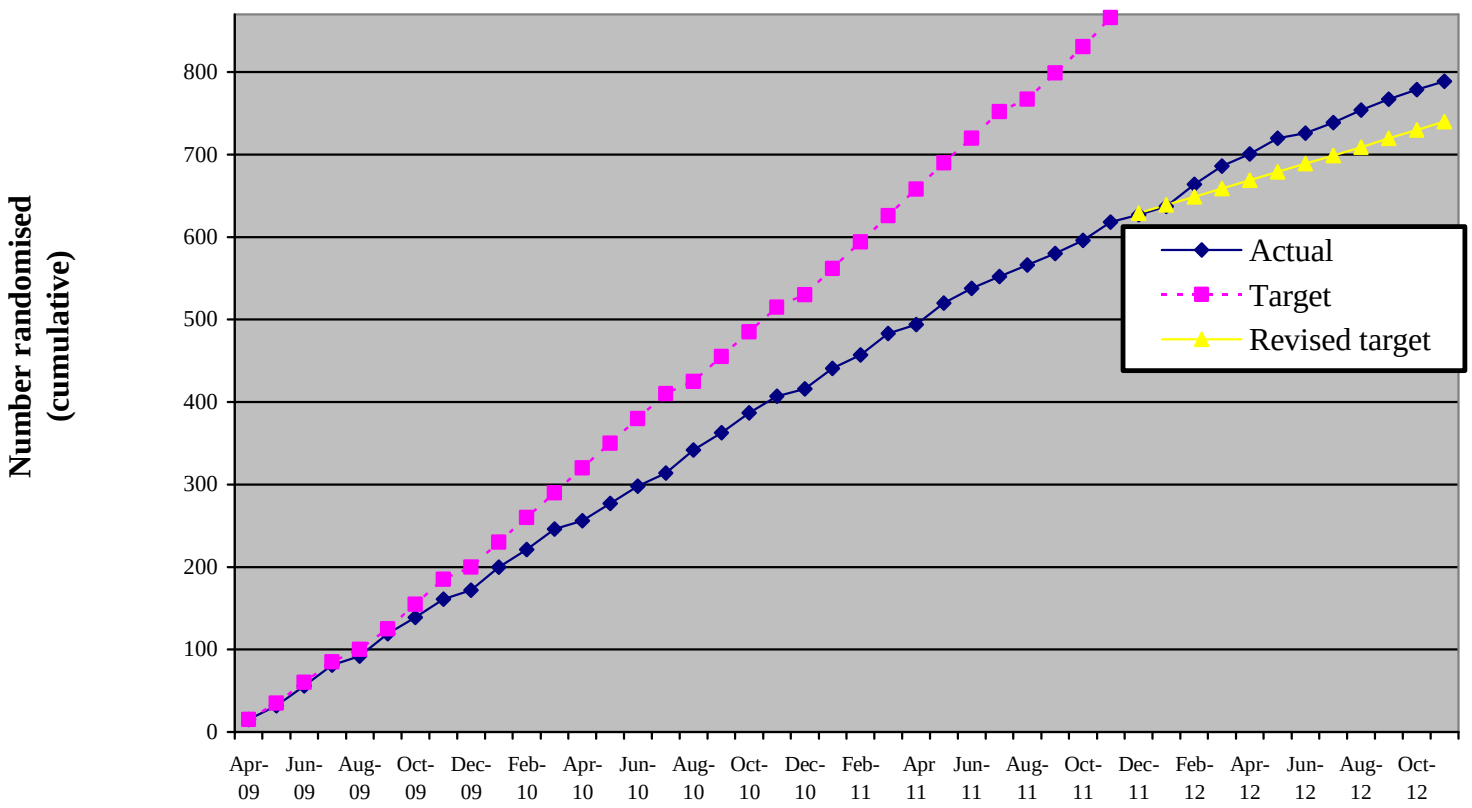


Table 4. Recruitment numbers by study centre

Centre	**Physical activity group** (n=393)	**Control group** (n=392)	**Total** (n=785) n (%)
St George's Healthcare NHS Trust (St George's Hospital)	44	44	88 (11.2)
Chelsea and Westminster Hospital NHS Foundation Trust (Chelsea and Westminster Hospital)	26	25	51 (6.5)
Imperial College Healthcare NHS Trust (Queen Charlotte's and Chelsea Hospital)	78	76	154 (19.6)
Imperial College Healthcare NHS Trust (St Mary's Hospital)	52	51	103 (13.1)
Guy's and St Thomas' NHS Foundation Trust (St Thomas's Hospital)	21	22	43 (5.5)
Croydon Health Services NHS Trust (Croydon University Hospital)	38	37	75 (9.6)
Kingston Hospital NHS Trust (Kingston Hospital)	40	41	81 (10.3)
Epsom and St Helier University Hospitals NHS Trust (Epsom Hospital)	47	46	93 (11.8)
Surrey and Sussex Healthcare NHS Trust (Crawley Hospital)	20	20	40 (5.1)
King's College Hospital NHS Foundation Trust (King's College Hospital)	5	5	10 (1.3)
Medway Foundation Trust (Medway Maritime Hospital)	6	7	13 (1.7)
West Middlesex University Hospital NHS Trust (West Middlesex Hospital)	8	10	18 (2.3)
Mid Cheshire Hospitals NHS Foundation Trust (Leighton Hospital)	7	9	16 (2.0)

Table 5. Recruitment methods

	%	n (total 785)
Midwife referral	69.3	544
Direct calling after consulting PAS	27.1	213
Flyer/Poster	1.3	10
Ultrasound questionnaire	1.4	11
Referral from PCT or other health professional	0.9	7

PAS: Patient administration system PCT: Primary care trust

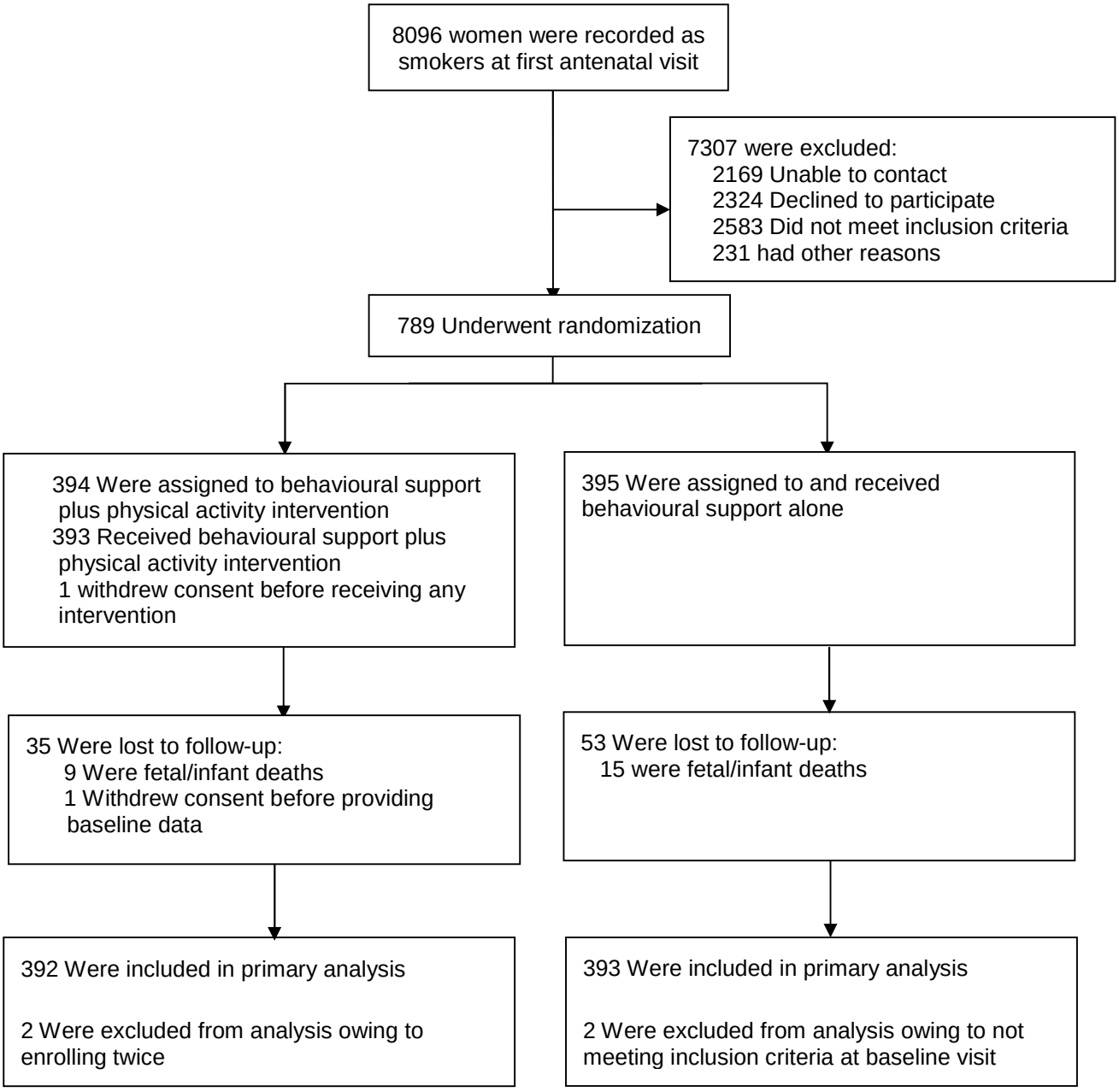


Figure 2. Numbers of participants who were enrolled in the study and included in the primary analysis The participants lost to follow-up included some who had fetal or infant loss and were not assessed for smoking status.

Table 6. Reasons for exclusion

	%	n (total 2583)
Reports smoking <1 cigarette a day now	27.5	710
Gestation >= 24 wks	26.1	673
Gestation < 10 wks	8.0	207
Unable to attend all visits	13.9	359
Wants to use NRT from commencing quit attempt	11.2	290
Poor English	5.8	149
Drug or alcohol problem	3.1	80
Reports smoking <10 cigarettes a day before pregnancy	2.1	53
Medical contra-indication for exercise	1.2	31
Age <16 years	0.7	17
Unable to walk for 15 mins	0.5	13
No permission to contact GP/obstetrician	0.03	1

NRT: Nicotine replacement therapy

Table 7. Baseline characteristics, according to study group

	Physical activity group (N = 391¶) Mean (±SD)	**Control group (N = 393) Mean (±SD)**
Age – yr	27.2 (±6.1)	27.8 (±6.5)
Age at leaving full-time education – yr¶¶	17.8 (±3.0)	18.0 (±3.3)
Weight - kg*	69.2 (±14.1)	70.9 (±15.9)
Body Mass Index - kg/m^2*	25.6 (±5.0)	26.6 (±5.6)
Gestational age – wk	15.6 (±3.3)	15.6 (±3.3)
	Median (IQR)	**Median (IQR)**
No. cigarettes smoked daily before pregnancy	20 (12-20)	20 (12-20)
No. cigarettes smoked daily at randomization	10 (5-12)	10 (5-15)
Fagerström Test of Cigarette Dependence score**	4 (2-5)	4 (2-5)
Expired carbon monoxide (CO) level – ppm***	10 (7-14)	10 (6-14)
Self-report of weekly moderate-vigorous intensity physical activity– mins	210.0 (125-350)	225.0 (130-360)
	n (%)	**n (%)**
Married or living with partner	230 (58.8)	221 (56.2)
Women with partner who smokes§§	261(66.8)	250 (63.6)
Caucasian†	308 (78.8)	298 (75.8)
Professional/managerial occupation	46 (11.8)	53 (13.5)
Smoked in a previous pregnancy¶¶¶	186 (78.2)	193 (77.5)
Edinburgh Post-natal Depression Scale score >15	43 (11.0)	40 (10.2)
Self-report of > 150 mins week of moderate to vigorous intensity physical activity	275 (70.3)	273 (69.5)
Self-report walking as the main type of physical activity	301 (77.0)	313 (79.6)
Parity§		
0-1	317 (81.1)	309 (78.6)
2-3	67 (17.1)	75 (19.1)
>4	7 (1.8)	9 (2.3)

Previous preterm birth††	68 (17.4)	61(15.5)
Very or extremely high confidence for quitting smoking	89 (22.8)	98 (24.9)
Very or extremely confident of doing 30 mins of physical activity on at least 5 days a week during pregnancy	274 (70.1)	277 (70.5)
Takes alcohol > twice a week	6 (1.5)	5 (1.3)
Consumes >3 alcoholic drinks on a drinking day§§§	14 (15.9)	3 (3.8)

IQR denotes interquartile range.

¶ Baseline data was not recorded for one participant in the physical activity group who withdrew consent shortly after randomization.

¶¶ Data exclude 41 women who were still in full-time education.

* Weight/BMI was not recorded for one participant in the control group.

** Fagerström Test of Cigarette Dependence score was not recorded for one participant in the physical activity group.

*** CO was not recorded one participants in the physical activity group and two in the control group.

§ Parity was defined as the number of previous pregnancies progressing beyond 24 weeks.

† Race or ethnic group was self-reported and categorized according to standard U.K. Census categories.

¶¶¶ Excludes 297 who had no previous pregnancies.

†† Previous preterm birth was defined as any previous pregnancy that lasted from 24 to 37 weeks.

§§ Excludes 92 women who had no partner.

§§§Excludes 617 women responding ‘not applicable’ (ie not taking alcohol).

Attendance at treatment sessions and compliance with physical activity intervention

Participants attended a median of four of 14 treatment sessions in the PA group and three, out of six, in the control group (*see Table 8*). For the physical activity group compared with the control group, there was a 40% (95% CI: 13%, 73%), 34% (6%, 69%) and 46% (12%, 91%) significantly greater increase in self-reported minutes of moderate to vigorous intensity physical activity (MVPA) from baseline to one week, four weeks and six weeks, respectively (*see Table 8 and Figure 3*). There was a decrease in self-reported minutes of PA at the end of pregnancy and six months, relative to baseline, for both groups. However, at end of pregnancy these reports were still 29% (95% CI: 5%, 60%) higher in the PA group relative to the control group, and these reached statistical significance (*see Figure 3 and Table 8*).

Of 90 participants asked to wear an accelerometer, 78 (86.7%) provided valid data (37 PA group), 10 provided insufficient data and two were technical failures. Participants providing accelerometer data had similar baseline characteristics to those in the total sample. The majority (72%) had valid accelerometer data for at least four days. During the week of accelerometer wear, the median (IQR) minutes of MVPA per day by self-report and by accelerometer was 38.2 (25.4-54.5) and 7.8 (0-16.5), respectively. Eighty seven-percent of participants self-reported higher levels of MVPA compared with the accelerometer. Self-reports of minutes of MVPA per day were not significantly correlated with the accelerometer data (Spearman's rho=0.133, p=0.247). Consistent with the correlation, using a Bland-Altman plot the mean difference (95% CIs) between the self-report and accelerometer data for MVPA was 26.85 (20.81-32.88) minutes (*see Figure 4*). There was no significant difference in accelerometer daily minutes of MVPA for the PA versus control group (Mann-Whitney u=692.5, p=0.386).

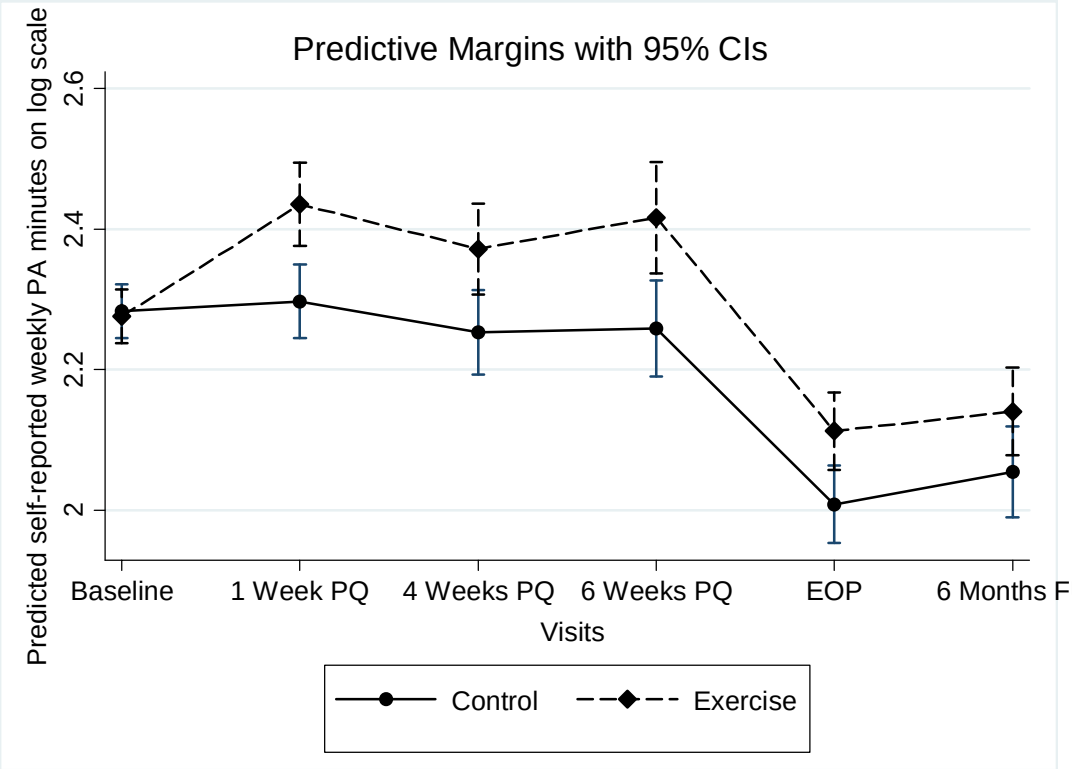
Only 28 women reported receiving face-to-face behavioural support for smoking cessation, besides that offered in the trial, and 60 women reported using NRT; the numbers reporting this support were similar in the two groups.

Table 8. Compliance to interventions

	Physical activity group N, Median (IQR)	**Control group N, Median (IQR)**	**Relative change of PA (95% CI): Mixed effect model for the log of PA**	**p value**
Self-reported weekly minutes of MVPA				
Baseline	391, 210 (125-350)	393, 225 (130-360)		
1 week post-quit	162, 280 (190-425)	206, 240 (140-420)	1.40 (1.13, 1.73)	0.002
4 weeks post-quit	135, 270 (180-420)	157, 210 (120-340)	1.34 (1.06, 1.69)	0.015
6 weeks post-quit	90, 277.5 (180-400)	121, 220 (130-350)	1.46 (1.12, 1.91)	0.005
End of pregnancy	188, 155 (100-240)	187, 140 (60-240)	1.29 (1.05, 1.60)	0.005
6 months follow up	147, 180 (80-330)	136, 135 (60-285)	1.24 (0.98, 1.57)	0.073
Number of treatment sessions attended	391, 4 (2-8)	393, 3 (2-6)	NA	
	N, Mean (±SD)	**N, Mean (±SD)**		
Time walked in mins on treadmill during supervised exercise				
Baseline	390, 12.2 (±7.5)	NA	NA	
1 week post-quit	163, 19.0 (±8.5)			
4 weeks post-quit	134, 15.2 (±10.8)			
6 weeks post-quit	90, 17.7 (±10.9)			

PA: Physical activity, MVPA: Moderate to vigorous intensity physical activity

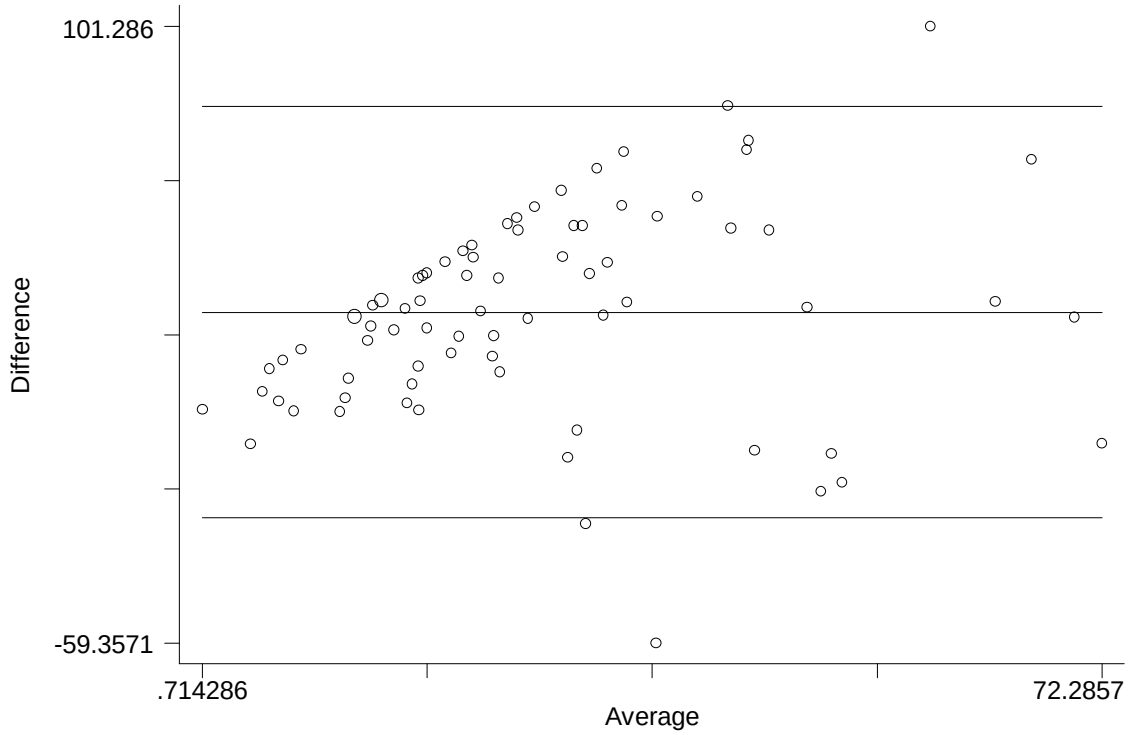
Figure 3: Comparison[a] of self-reported levels of moderate to vigorous intensity physical in trial groups at different time points



PA: Physical Activity, PQ: Post Quit, EOP: End of pregnancy, FU: Follow up

[a]Prediction on log scale from the mixed-effect model.

Figure 4. Bland-Altman plot of the difference between self-reported MVPA and accelerometer data for MVPA against the average of these measures (N=78) showing the difference versus the average, showing the distribution of differences and how they relate to average.



Limits of agreement (reference range for difference): -26.698 to 80.390

Range: 0.714 to 72.286

MVPA: Moderate-to-vigorous intensity physical activity

Smoking abstinence and reduction rates

There was no significant difference in smoking abstinence rates or smoking reduction rates between the two groups at follow-up (*see Table 9*). The rate of validated continuous abstinence at end of pregnancy (primary outcome) was 7.7% in the PA group and 6.4% in the control group (odds ratio for PA group, adjusted for centre only, 1.21; 95% CI, 0.70 to 2.10). At four weeks, the validated abstinence rate was 12.8% in the PA group and 15.5% in the control group (odds ratio, adjusted for centre only, 0.79; 95% CI, 0.53 to 1.18). At six months postnatally the self-reported abstinence was 6.1% in the PA group and 4.1% in the control (odds ratio, adjusted for centre only: 1.55; 95% CI, 0.81 to 2.97). Fully adjusted analyses yielded similar findings (at end of pregnancy: OR (95% CIs): 1.37 (0.78 to 2.41)). The sensitivity analyses showed that the observed effect size and its statistical significance was independent of the influence of missing

data for the primary outcome. There was no significant interaction between baseline self-reports of MVPA (<150 vs ≥ 150 minutes/week physical activity) and the treatment effect for the primary outcome (logistic regression model adjusted for site only: likelihood-ratio test (LR chi-squared = 2.31, p = 0.129, similar results were found for the fully adjusted model). Nor was there any evidence that PA adherence in the PA group, indicated by a change from reporting <150 minutes MVPA at baseline to reporting ≥ 150 minutes MVPA at four or six weeks post-quit, was significantly associated with smoking abstinence at those times (adjusted for site only: at four weeks: OR (95% CI) = 0.74 (0.10 to 5.30), p=0.762); at six weeks: OR (95% CI) = 0.63 (0.05 to 7.83), p=0.720).

Withdrawal symptoms and urge to smoke

Tables 10 and 11 show the withdrawal symptom and urge to smoke scores for baseline and one week post-quit. Relative to baseline, the change in the withdrawal symptoms total score and the urge to smoke score at one week post-quit did not differ significantly between the two study groups. For the PA group, compared with the control group the difference in the withdrawal symptoms change score was 0.5 (95% CI: -0.5, 1.7, p=0.294) and for the urge to smoke change score it was 0.3 (95% CI: -0.2, 0.7, p=0.266). When withdrawal symptoms were examined individually there was still no significant difference in change scores between the groups at this time.

Confidence for taking physical activity and stopping smoking

Tables 12 and 13 present the scores for confidence for taking PA and for stopping smoking, respectively, at baseline and one week post-quit. Between baseline and one week post-quit, there was a significant difference in ratings for confidence for taking PA, for the PA versus control group (p=0.005). The difference between the PA and control groups in the confidence for PA change score was -0.3 (95% CI: -0.6 to -0.1), with confidence remaining unchanged in the PA group and decreasing in the control group. There was no significant difference between the groups in for confidence for quitting smoking (difference: -0.2, 95% CI: -0.4 to 0.02).

Table 9. Primary and secondary smoking abstinence and reduction outcomes

Abstinence outcomes	Physical activity group (N = 392) n (%)	Control group (N = 393) n (%)	Odds Ratio (95% CI) †	Adjusted Odds Ratio (95% CI) ‡
Primary				
Self-reported continuous abstinence[a] at end of pregnancy[b] with biochemical validation[c]§	30 (7.7)	25 (6.4)	1.21 (0.70, 2.10)	1.37 (0.78, 2.41)
Secondary				
Self-reported continuous abstinence at 4 weeks after quit day with validation.§§	50 (12.8)	61 (15.5)	0.79 (0.53, 1.18)	0.87 (0.57, 1.31)
Self-reported continuous abstinence at 6 months after birth.	24 (6.1)	16 (4.1)	1.55 (0.81, 2.97)	1.66 (0.82, 3.37)
Self-reported lapse free abstinence with validation:				
At 4 weeks after quit day.	17 (4.3)	16 (4.1)	0.68 (0.38, 1.22)	0.74 (0.41, 1.34)
At end of pregnancy.	20 (5.1)	29 (7.4)	1.07 (0.53, 2.14)	1.22 (0.60, 2.48)
At 6 months after birth.	10 (2.6)	10 (2.5)	1.04 (0.43, 2.56)	1.12 (0.45, 2.78)
Self-reported reduction in number of cigarettes smoked daily[d]	**Physical activity group N, Mean (SD)**	**Control group N, Mean (SD)**	**Mean difference 95% CIs**	**Mean difference 95% CIs**
Between baseline and 4 weeks after quit day.	67, 4.3 (4.4)	70, 4.0 (4.7)	0.23 (-1.22, 1.73)	0.27 (-1.16, 1.65)
Between baseline and end of pregnancy.	130, 4.0 (4.7)	119, 2.9 (5.9)	1.13 (-0.26, 2.55)	1.08 (-0.11, 2.32)

Between baseline and 6 months after birth.	97, 1.4 (4.5)	100, 1.0 (5.3)	0.37 (-0.99, 1.74)	0.21 (-1.14, 1.58)

† Odds ratios were adjusted for recruitment centre only (as a stratification factor).
‡ Odds ratios were adjusted for centre, Fagerstrom Test of Cigarette Dependence score at baseline, participant age at randomisation, Edinburgh Post-natal Depression Scale score at baseline, age at leaving full-time education and partner's smoking status at baseline.
[a]Continuous abstinence is defined as having smoked less than five cigarettes since the quit day.
[b]End of pregnancy is defined as between 36 weeks gestation and 10 weeks after the birth.
[c]Validated by either exhaled carbon monoxide and/or salivary cotinine, if both measures were available both were required for validation.
§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in 12 of 42 women (28.6%) in the physical activity group and in 19 of 44 (43.2%) in the control group.
§§The biochemical tests did not validate the report of not smoking in 4 of 51 women (7.8%) in the physical activity group and in 7 of 61 (11.5%) in the control group.
[d]Using linear regression analysis with bootstrap method.

Table 10. Comparison of withdrawal symptom scores between randomization groups at baseline and one week post quit

Visit	Variable/measures	Randomization groups		p-value[a]
		Physical Activity n, Mean (SD)	**Control n, Mean (SD)**	
Baseline	Withdrawal symptoms scale total score (1-35)	391, 16.3 (4.9)	393, 16.4 (4.7)	
Symptoms	Restless	2.3 (1.2)	2.3(1.2)	
	Irritable	2.6 (1.2)	2.7 (1.2)	
	Depressed	1.8 (1.1)	1.7 (1.0)	
	Hungry	2.8 (1.3)	3.0 (1.2)	
	Poor concentration	2.0 (1.1)	2.0 (1.1)	
	Poor sleep at night	2.5 (1.3)	2.5 (1.3)	
	Anxious	2.2 (1.2)	2.2 (1.2)	
1 week post-quit	Withdrawal symptoms scale total score (1-35)	163, 16.0 (4.6)	206, 16.6 (4.6)	
Symptoms	Restless	2.4 (1.1)	2.4 (1.1)	
	Irritable	2.7 (1.1)	2.9 (1.2)	
	Depressed	1.7 (1.0)	1.8 (1.0)	
	Hungry	2.7 (1.2)	2.9 (1.2)	
	Poor concentration	2.1 (1.0)	2.1 (1.1)	
	Poor sleep at night	2.3 (1.2)	2.3 (1.2)	
	Anxious	2.1 (1.0)	2.2 (1.1)	
	Change of withdrawal symptoms scale total score relative to baseline	-0.3 (5.0)	0.2 (5.5)	0.294

[a]p value was calculated using a t-test

Table 11. Comparison of urge to smoke scores between randomization groups at baseline and one week post quit

Visit	Measures	Randomization groups		p-value[b]
		Physical Activity n, Mean (SD)	Control n, Mean (SD)	
Baseline	Urge to smoke in the past week score[a] (0-10)	391, 6.2 (2.0)	393, 6.2 (1.9)	
1 week post-quit	Urge to smoke in the past week score[a] (0-10)	163, 5.3 (2.0)	206, 5.5 (2.0)	
	Change of urge to smoke score	-0.7 (2.3)	-0.4 (2.4)	0.266

[a]Combination of item for strength of urges plus item for frequency of urges.

[b]p value is calculated from a t-test

Table 12. Comparison of self-confidence for taking physical activity between randomization groups at baseline to one week post-quit

Visit	Measures	Randomization groups		p-value[a]
		Physical Activity (N=392)	Control (N=393)	
Baseline	N Mean (SD)	391 3.9 (1.1)	393 3.9 (1.0)	
1 week post-quit	N Mean (SD)	163 3.9 (1.0)	157 3.7 (1.0)	
	N Mean (SD) change from baseline	163 -0.01 (1.1)	157 -0.3 (1.0)	0.005

[a]Using a t-test

Table 13. Comparison of self-confidence for stopping smoking between randomization groups at baseline to one week post-quit

Visit	Measures	Randomization groups		p-value[a]
		Physical Activity (N=392)	Control (N=393)	
Baseline	N Mean (SD)	391 3.9 (0.9)	393 4.0 (1.0)	
1 week post-quit	N Mean (SD)	163, 4.4 (1.0)	206 4.3 (0.9)	
	N Mean (SD) change from baseline	163 (0.4) (1.1)	206 0.2 (1.1)	0.074

[a]Using a t-test

Birth outcomes

Table 14 shows outcomes for singleton births including deaths, mean birth weight, rates of preterm birth, low birth weight, neonatal admissions, apgar scores, cord-blood arterial pH, congenital abnormalities and mode of delivery. These were very similar in the two study groups, except there were significantly less deliveries by caesarean section in the PA group than in the control group (28.7% versus 21.3%, p<0.023). Analyses that included twin births gave very similar findings.

Adverse events

There were similar numbers of adverse events and serious adverse events in the two groups (*see Table 15*). The total number of women or their infants who had at least one AE or SAE was 217 (55.4%) in the PA group and 219 (55.7%) in the control group (OR 95% CI= 0.99, 0.75, 1.32). The full breakdown of the data for less frequent adverse events presented in *Appendix 8.*

Table 14. Birth outcomes by treatment group[a]

Fetal outcomes (singleton births only)	**Physical activity group N=384**	**Control group N=391**	
	no/total no (%)	**no/total no (%)**	**OR (95% CI)[b]**
Miscarriage[c]	6/383 (1.6)	10/389 (2.6)	0.60 (0.22 to 1.67)
Stillbirth[c]	2/377 (0.5)	2/379 (0.5)	1.01 (0.14 to 7.24)
Neonatal death[c]	0	1/391 (0.3)	Not calculated
	Mean (SD)	**Mean (SD)**	**Mean difference (95% CI)[b]**
Birth weight (kg)	n=354 3.13 (0.58)	n=359 3.15 (0.64)	-0.01 (−0.11 to 0.07)
Gestational age at delivery (weeks)	n=356 39.24 (2.1)	n=348 39.26 (2.1)	-0.02 (-0.36 to 0.31)
	no/total no (%)	**no/total no (%)**	**OR (95% CI)[b]**
Preterm birth (<37 weeks gestation)	35/356 (9.8)	26/348 (7.5)	1.36 (0.78 to 2.31
Low birth weight (<2.5kg)	44/359 (12.3)	38/353 (10.8)	0.87 (0.55 to 1.38)
Neonatal intensive care unit admission	27/352 (7.7)	36/356 (10.1)	0.74 (0.44 to 1.25)
Apgar score at 5 minutes < 7	11/351 (3.1)	8/336 (2.4)	0.74 (0.29 to 1.85)
Cord-blood arterial pH < 7	2/125 (1.6)	0/125	Not calculated
Congenital abnormalities[d]	9/345 (2.6)	6/348 (1.7)	1.44 (0.50 to 4.13)
Assisted vaginal delivery	46/357 (12.9)	32/359 (8.9)	1.51 (0.94 to 2.43)
Caesarean delivery	76/357 (21.3)	103/359 (28.7)	0.67 (0.48 to 0.95)*

[a] For all outcomes, 10 women with twins (8 in physical activity group) were removed from the denominator.

[b] Odds ratios and mean differences were adjusted for recruitment centre (as a stratification factor).

[c] These outcomes were defined *a priori* as serious adverse events. There were no maternal deaths and no serious adverse events were judged to be related to the physical activity intervention. The denominator for miscarriage was calculated as the number randomized minus the number of

elective terminations (n=3) (elective terminations are excluded as they do not have the potential to miscarry). The denominator for stillbirth was calculated as the number randomized minus the number of miscarriages and elective terminations (elective terminations and miscarriages were excluded as they do not have the potential to result in a stillbirth). For all other outcomes, the denominator is the number of singleton live births, excluding those births for which outcome data were missing.

[d] For a list of congenital abnormalities *see Appendix 8.*

*p<0.023

Table 15. Adverse Events (AEs), according to Study group*

Event	**Physical activity group (N = 392) n (%)**	**Control group (N = 393) n (%)**
Serious adverse events — no. (%)		
Maternal death	0	0
Other events†	12 (3.1)	13 (3.3)
Maternal AEs potentially related to treatment††	2 (0.5)	0
Maternal AEs as probable complications of pregnancy		
Vaginal bleeding or haemorrhage	37 (9.4)	35 (8.9)
Abdominal pain	79 (20.2)	83 (21.1)
Infection in pregnancy	61 (15.6)	55 (14.0)
Premature rupture of membranes at <37 weeks gestation	19 (4.8)	16 (4.1)
Gestational diabetes	7 (1.8)	8 (2.0)
Gestational hypertension	13 (3.3)	13 (3.3)
Preeclampsia	4 (1.0)	11 (2.8)
Other, less frequent events**	105 (26.8)	114 (29.0)
Fetal AEs as probable complications of pregnancy		
Decreased fetal movement	41 (10.5)	49 (12.5)
Intrauterine growth restriction	15 (3.8)	18 (4.6)
Other, less frequent events**	7 (1.8)	6 (1.5)
Neonatal adverse events	15 (3.8)	14 (3.6)
Total Adverse events	416	436

*For each study group, percentages were calculated as the number of women who had at least one event in any category of adverse event, divided by the number of women who underwent randomization. Participants may have had adverse events in more than one category.
†Other serious adverse events included miscarriage, stillbirth, and neonatal deaths, plus events resulting in a significant disability or incapacity and/or is life-threatening
†† Spotting, nausea
**Events occurred in less than 3% of women or infants; for a list of these *see Appendix 8.*

Maternal depression

All 784 participants provided EPDS scale data at baseline, 383 (48.9%) and 268 (34.2%), respectively, provided these data at follow-up at the end of pregnancy and six-months postnatally. The baseline characteristics of the sub-samples used for the EPDS analysis at the two follow-up points were similar as for the total trial sample (see Table 16). The baseline characteristics of the two trial groups were also similar in the sub-samples at end of pregnancy and at six months postnatally.

Table 16. Comparison[a] of depression scores in two trial groups at end of pregnancy and six months after birth

Visit time	EPDS score Mean (SD)		β (difference between PA and control group, adjusted for baseline EPDS only) (95% CI)[b]	β (difference between PA and control group, adjusted for baseline EPDS and all other predictors[b]) (95% CI)[c]
	Control group	Physical activity group		
baseline	7.7 (5.0)	7.6 (5.3)	0	0
End of pregnancy	7.2 (5.0)	8.0 (4.9)	1.21 (0.17, 2.01)	1.19 (0.15, 1.95)
6 months follow-up	6.7 (4.7)	6.7 (4.7)	0.48 (-0.65, 1.35)	0.43 (-0.67, 1.28)

EPDS=Edinburgh Postnatal Depression Scale, PA=Physical activity
[a]Results from mixed effect linear model
[b]Adjusted for age at leaving full time education, young age (≤ 20 yrs), BMI, marital status.
[c]Bootstrapped method: bias-corrected confidence intervals.

In both models, EPDS score was significantly higher in the PA group versus the control group at end of pregnancy (*see Table 16*). At this time, there was a mean increase in EPDS score of 0.4 in

the PA group and a mean reduction of 0.5 in the control group (mean difference between groups (95% CIs) in fully adjusted model: 1.19 (0.15 to 1.95)). When examining the data separately for 'end of pregnancy' outcomes before and after the birth the findings were very similar. There was no significant difference in EPDS score between the groups at six months follow-up (fully adjusted mean difference (95% CIs): 0.43 (-0.67 to 1.28).

Maternal weight

The combined sample for the analysis of maternal weight at 'end of pregnancy' was 263 participants, with 139 (52.9%) providing maternal weight before the birth and 124 (47.2%) after the birth. The characteristics of these two sub-samples (i.e. before and after birth) were comparable to the main LEAP trial sample, except that the rate of continuous smoking abstinence at end of pregnancy was higher in both the subsample with maternal weight before delivery and that after delivery (no. (%) abstinent: 35 (25.2); 12 (9.7), respectively), compared with the main sample (55 (7.0%). In the combined sample at end of pregnancy, the characteristics were very similar between the two randomization groups, except there was about a 1 kg difference of weight at early pregnancy between the two groups and therefore the results were adjusted for weight at early pregnancy. Rates of smoking abstinence were slightly higher for the PA than the control group at end of pregnancy (no. (%) abstinent: 27 (20.3), 20 (15.4)), but this difference was not significant. When comparing the characteristics between the randomization groups separately for the sub-samples before and after the birth the findings were very similar.

At the end of pregnancy, the mean (SD) gestational weight gain (kg) (sub-sample before birth) for physical activity group (PA) was 12.4 (6.1) and for the control group was 11.1 (7.1), and the postnatal weight retention (kg) (sub-sample after birth) was 4.6 (7.4) and 5.3 (7.2) respectively. The unadjusted mean difference of gestational weight gain before birth and postnatal weight retention for the physical activity group versus control was 1.33 (95% CI, -0.85 to 3.52) and -0.71 (95% CI, -3.28 to 1.87), respectively. When adjusting for potential prognostic factors, these mean differences were reduced (*see Table 17*) and neither unadjusted nor adjusted analyses achieved statistical significance. The estimated mean (SD) weight change (kg) per gestation week was 0.31 (0.15) for the PA group and 0.26 (0.17) for control, and the difference was not significant. While the weight change per gestation week was significantly lower for those classed as obese versus non-obese at baseline (-0.12kg; 95% CI, -0.21 to -0.03). There was no significant interaction between the effect of PA versus control and whether the individual was obese at baseline (0.03kg; 95% CI, -0.10 to 0.17, p = 0.628) such that in those who were not obese, the difference between PA and control groups was (0.03kg; 95% CI: -0.03, 0.09) whilst in

those who were obese the difference between PA and control groups was (0.06kg; 95% CI: -0.09, 0.21).

According to IOM guidelines[63], the overall proportion of women with excessive gestational weight gain was 38.1%. The risk of excessive gestational weight gain was slightly higher in the PA group versus control (adjusted odds ratio, 1.33; 95% CI, 0.63 to 2.80), but the difference was not significant (*see Table 17*). The risk was significantly higher for the overweight and obese categories versus healthy weight (adjusted ORs, 95% CIs: 3.86, 1.63 to 9.16; 3.77, 1.42 to 9.96, respectively). Those in the underweight category were less likely to gain excessive gestational weight compared with those of a healthy weight but this was not significant (adjusted OR 95% CIs: 0.61, 0.07 to 5.71). As sensitivity analyses, when adjusted for the effect of baby's weight and rates of smoking abstinence, the mean difference of the weight change between the two groups was slightly changed and the effect of baby's weight was significant in the regression models (*see Table 17*).

Table 17. Comparison of maternal weight change (kg) between early pregnancy and 'end of pregnancy' (separate analysis for subsamples before and after delivery) by randomisation group

Sub-sample at end of pregnancy with maternal weights measured before birth (N= 139)				
Variables	PA group Mean (SD) n=74	Control group Mean (SD) n=65	Unadjusted mean difference PA versus control (95% CI)*	Adjusted mean difference of PA versus control (95% CI)**
Early pregnancy weight EOP weight Weight change	68.27 (14.4) 80.70 (14.9) 12.43 (6.1)	70.37 (15.6) 81.47 (14.8) 11.10 (7.1)	1.33 (-0.85, 3.52)	0.92 (-1.15, 2.99) 0.99 (-0.98, 2.95)[s]
Weight change per gestation week	0.31 (0.15)	0.26 (0.17)	0.05 (-0.01, 0.10)	0.02 (-0.03, 0.08)† 0.02 (-0.04, 0.07)†[s]
	n (%)	n (%)	Unadjusted OR (95% CI)§	Adjusted OR (95% CI) §§
Excessive gestation weight relative to early pregnancy BMI	30 (40.5)	23 (35.4)	1.25 (0.63, 2.48)	1.33 (0.63, 2.80) 1.36 (0.61, 3.05)[s]
Sub-sample at end of pregnancy with maternal weights measured after birth (N= 124)				
	Mean (SD) n=59	Mean (SD) n=65	Unadjusted mean difference of PA versus control (95% CI)*	Adjusted mean difference of PA versus control (95% CI)**
Early pregnancy weight EOP weight Weight change	66.08 (14.8) 70.65 (14.1) 4.56 (7.4)	66.05 (12.8) 71.33 (13.2) 5.27 (7.2)	-0.71 (-3.28, 1.87)	-0.73 (-3.15, 1.69) -0.57 (-2.95, 1.82)[s]

EOP: End of pregnancy; PA: Physical activity; BMI: Body mass index

*****Linear regression model with maternal weight change at EOP as dependent variable and randomisation groups as independent variable.

******In multivariate linear regression models, adjustment for age, number of previous pregnancies and weight at early pregnancy,

[s]Sensitivity analysis: In all analyses, further adjustment for continuous smoking abstinence at EOP and baby's weight. Sample sizes for these analyses are n=133 (sub-sample before birth) and n=120 (sub-sample after birth) due to missing data in baby's weight and excluding twins.

†Adjusted for an interaction between obese versus non-obese at baseline and effect of PA versus control, in addition to age and number of previous pregnancies.

§Logistic regression with excessive gestation weight relative to early pregnancy BMI (yes, no) as dependent variable and randomisation groups as independent variable.

§§Adding the BMI categories at early pregnancy (healthy weight, underweight, overweight and obese) to the above model and adjusting for age, number of previous pregnancies.

CHAPTER 4: HEALTH ECONOMICS ANALYSIS AND RESULTS

Introduction

Several studies have investigated the potential cost saving of smoking cessation interventions in pregnancy[90] but only one study could be identified which has used empirical data on costs to calculate the incremental cost effectiveness of these interventions.[91] This chapter reports on an economic evaluation conducted alongside the LEAP trial, addressing the cost-effectiveness of a PA intervention plus behavioural support, compared with behavioural support alone.

The objectives were:

1. To compare the costs associated with the control and intervention strategies.
2. To estimate the consequences of these alternatives.
3. To assess the cost-effectiveness of PA intervention used in addition to behavioural support on smoking cessation at the end of pregnancy.

Methods

Overview

A cost-effectiveness analysis was undertaken to compare a PA intervention plus behavioural support with behavioural support only, for women who were smoking in pregnancy. The main outcome for the economic evaluation was biochemically validated abstinence from smoking between a quit date and end of pregnancy. As recommended by NICE,[92] cost utility analyses with fully incremental analyses were conducted from an NHS and personal social services viewpoint, including direct health effects (maternal smoking cessation) and costs (or cost savings) to the NHS. Women were eligible for inclusion in the LEAP trial if they were between 10 and 24 weeks gestation and outcomes were collected at end of pregnancy (between 36 weeks gestation and 10 weeks post-partum), therefore the time horizon of the trial was up to 9 months. A clinical trial of nicotine replacement therapy for smoking cessation (SNAP) was approved by NIHR HTA shortly before this study began[93,94] and as both studies used similar outcome measures, a similar approach has been taken to economic evaluation to permit comparison.

Cost estimation

Two main costings were included; first, the costs of the interventions and, secondly, the costs of caring for each woman and her infant during the period between randomisation and the immediate post-natal period (up to six weeks post-partum).

Intervention costs

The cost for the interventions included training and time for staff (costed as Band 6 midwives, including overheads) to deliver the behavioural support and physical activity consultations (carbon monoxide (CO) monitors (breath testing equipment), consumables associated with CO breath testing, equipment (treadmills, and pedometers to count steps when walking), exercise DVDs, printing of PA manual for participants and childcare. Participants in both arms were offered up to six sessions of behavioural support for smoking cessation. In addition, those in the PA arm were offered 14 sessions of supervised treadmill exercise and nine PA consultations, which were combined with the smoking cessation support. All the support was face-to-face. The time spent providing support in the LEAP trial was multiplied by salary and overhead costs to calculate a cost per session.

The costs per use of CO monitoring in the LEAP trial (*see Table 18*) were calculated by first totalling the costs of equipment and consumables and dividing these by the total number of uses. The equipment and consumables included: 12 CO monitors (two calibration kits, semi-disposable mouth pieces (assuming that these were changed every 60 uses), batteries (assuming they were changed every 210 uses) and mouth pieces per each use and alcohol free wipe per use. Assumptions concerning the need to change semi-disposable mouth pieces and batteries were taken from the SNAP trial.[94]

It was assumed that a treadmill would last for 10 years and that three midwives would require training in that time; therefore annual costs were calculated as one tenth the cost of a treadmill and one tenth the cost of the training of three midwives, calculated as one day of PA training and one day of smoking cessation training for each midwife. Costs of training were derived from costs of training in the LEAP trial. In the control arm, only the cost of smoking cessation training was included. A Professor of Clinical Psychology provided the smoking cessation training, and a private PA consultant, specialising in exercise and pregnancy, delivered the physical activity training; both of these trainers regularly provide training in the NHS.

We wanted to present findings for an ‘average / typical’ hospital and so made the following additional assumptions: given a hospital with 5000 births per year with 600 (12%) pregnant smokers (based on national data)[7] and using the recruitment rate in the LEAP trial of 9.7% (785 of 8096 eligible women randomised), 58 (9.7% of 600) women be recruited annually. Therefore, per-participant costs for treadmill and training were estimated by dividing the annual costs by 58. The robustness of the results to this assumption was tested in sensitivity analysis.

Health care resource use costs

Information about antenatal and postnatal hospital admissions and mode of delivery was collected from maternal medical records, and data on admissions to neonatal special care came from infant medical records.

Valuation of costs

All data were valued in monetary terms and unit costs were reported in Pounds Sterling for the financial year 2012/13 (representing the end-point of the trial). Since follow-up did not continue beyond 9 months post-randomisation, the question of discounting future costs did not arise. For standard NHS health care, UK unit costs were applied from national sources, increasing the generalisability of the results. Table 18 presents a summary of resource use and unit costs.

Calculating costs

To calculate the cost of face-to-face support, for each trial participant, we multiplied the number of treatment sessions, by the duration of support in minutes. For the PA group, we assumed that the midwife only engaged with the woman when she was off the treadmill, except that during the first 5 minutes of each treadmill walking session the midwife provided some PA counselling; the estimate of 5 minutes is based on interviews with the researchers who provided the interventions. Besides these 5 minutes, for the rest of the time that the woman was on the treadmill the midwife was able to proceed with her normal work.

Example: Suppose that a patient has 11 treatment sessions lasting 471 minutes (including treadmill time) and uses the treadmill in 10 of these sessions for a total of 279 minutes. This patient will have spent 471-279=192 minutes in treatment sessions when not using the treadmill. It is assumed that the midwife contact time consists of these 192 minutes, plus a further 5 minutes for each of the 10 sessions in which a treadmill was used:

Total midwife time is (471-279) + (10 × 5) =242 minutes

The cost of mode of delivery was established by calculating a weighted average of unit costs for different modes of delivery activities recorded in NHS reference costs. A similar method was used to calculate an average cost of a maternal antenatal admission and postnatal admission, based on antenatal observations and investigations.

Table 18. Unit costs (2012/13 prices)

	Unit cost	Unit	Source of unit cost
Interventions			
Physical activity group only			
Treadmill	£775	Per treadmill	LEAP trial estimation
Pedometer	£7.12	Per pedometer	LEAP trial estimation
Printing	£0.58	9 page PA manual	LEAP trial estimation
Exercise DVDs	£0.80	Per DVD	LEAP trial estimation
PA training costs	£120	Per midwife trained	LEAP trial estimation
Both groups			
Smoking cessation training	£250	Per midwife trained	LEAP trial estimation
Band 6 (mid-point) midwife time (including OHs)	£31.95	Per hour	Curtis 2013[94]
CO monitors & consumables	£1.37	Per use	LEAP trial estimation
Childcare	£15	Per crèche visit	LEAP trial estimation
Health care use (both groups)			
Maternal antenatal admission	£582.24	Per day	Department of Health 2013[96]
Mode of delivery:		Per obstetric delivery	Department of Health 2013[96]
Unassisted vaginal delivery	£2, 313.60		
Assisted vaginal delivery	£2,788.86		
Caesarean section	£3,848.83		
Miscarriage	£1,376.76		Petrou et al 2006[a] [97]
Baby admission to neonatal unit (assumes an average of 4 days in hospital)	£2967.18	Per admission	Department of Health 2013[96]
Maternal post-natal admission	£782.68	Per day	Department of Health 2013[95]

[a]Average NHS cost of miscarriage management inflated to 2012-13 prices using the Hospital and Community Health Services Pay and Price Index.[95] PA: physical activity

To calculate the cost of a baby's admission to neonatal care, a weighted average of bed day costs for neonatal critical care taken from NHS reference costs was multiplied by a weighted average length of stay for neonates with major diagnoses derived from Hospital Episode Statistics for 2012-13.[96] The daily costs of antenatal and postnatal admissions were established by calculating a weighted average of daily unit costs of different healthcare resource group activities recorded in NHS reference costs. For settings with a length of stay longer than one day, information on bed days was used to calculate a weighted average daily cost. Quantities of services used were multiplied by the relevant unit costs to estimate overall cost profiles for women in the trial.

Outcome measures

The measure of health benefit for the economic evaluation was the same as for the primary measure of clinical effectiveness in the LEAP trial; self-reported and biochemically validated maternal smoking cessation from quit date to end of pregnancy. Temporary smoking lapses of up to a total of five cigarettes (on up to five occasions) were permitted.

Analysis

An incremental cost-effectiveness analysis was undertaken, following the NICE guidance for health care evaluations,[92] comparing the additional costs of a PA intervention compared with behavioural support alone, as well as the additional benefits, to give a cost per additional quitter.

Results have been presented first as per-participant quit rate and costs including fixed costs apportioned as described above under 'cost estimation'. The same results have also been scaled up to the expected annual costs and outcomes for a typical hospital with 58 participants per year as used for the estimation of fixed costs.

When two interventions are compared in a cost-effectiveness analysis, it may be the case that the more effective intervention is also the less costly. In that case, the strategy that is both more effective and less costly is said to *dominate* the other strategy. The dominating strategy is then unconditionally preferred regardless of any considerations of budget. When no dominance relationship exists, the results are summarised in the incremental cost effectiveness ratio (ICER), which is the additional cost of achieving one extra quitter. It can be calculated as the expected per-participant cost of the intervention group over and above the control, divided by the expected difference in quit rate. The following is the formula for the ICER, where Δ represents change, C represents the costs, E represents the effects, and subscripts I and C refer to the intervention and control, respectively.

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_I - C_C}{E_I - E_C}$$

(Note that when a dominance relationship exists, the ICER as calculated above is negative, but the numerical value is not informative. This can be seen because doubling either ΔC or ΔE makes the dominance relationship stronger, but these two possible changes have opposite effects on the numerical value of the ICER.)

A total of 785 women were included in the primary ITT analysis; 392 and 393 in the PA and control arms, respectively. However, one individual withdrew consent before providing any data or receiving any treatment and was, therefore, excluded from the economic evaluation. Thus, we analysed data for 391 in the PA group and 393 in the control group. Analyses were conducted in Microsoft Excel 2010.

There were no missing data on the effectiveness outcome (validated smoking cessation from quit date to end of pregnancy), as any women without validated cessation were assumed to be smokers. The average resource use of each cost item was estimated from the available data for the relevant arm of the trial, effectively imputing an average for each woman with missing data. This was justified following preliminary analysis which showed no significant association between any of the resource use items and key patient baseline characteristics associated with smoking cessation (age, Fagerstrom Test of Cigarette Dependence score (FTCD) Edinburgh Post-natal Depression Scale (EPDS) score, partners smoking status, age leaving full-time education), plus quit status at end of pregnancy. Age was significantly associated with mode of birth, such that those who were older were more likely to have a caesarean section. Also, those with a higher EPDS score were significantly more likely to report at least one antenatal hospital admission and one postnatal admission. However, as neither age nor EPDS score were significantly associated with smoking status at end of pregnancy these associations with resource use were not considered a concern when imputing missing data.

Bootstrapping was used to assess the joint uncertainty in cost and effectiveness outcomes. Missing data were imputed individually for the relevant resource use items to produce a complete data set. Then bootstrapped data sets of the same size as the original patient groups were constructed by sampling at random with replacement. Incremental cost and effectiveness estimates were then calculated using the same methods as described earlier. This was repeated 2000 times to produce a joint distribution of incremental cost and effectiveness, which was plotted on a cost-effectiveness plane.[98] A cost-effectiveness

acceptability curve[99] was generated showing the proportion of bootstrapped replications which would be cost-effective at a range of threshold incremental cost-effectiveness ratios.

The baseline characteristics of age and nicotine dependence are reliable predictors of smoking cessation. Therefore, in a subgroup analysis, cost effectiveness calculations were repeated using only data for the following subgroups: women under 28, women over 27, women with FTCD score<4, women with FTCD ≥4.

Results

In the PA group 30 of 391 women (7.7%) were abstinent with biochemical validation from quit date to end of pregnancy, and in the control group this was true for 25 of the 393 women (6.4%), a non-significant difference of 1.3% (*see Chapter 3 Results*).

Table 19 reports on health care resources utilised in the two arms of the trial. Quantities of services were multiplied by the relevant unit costs in Table 18, to calculate the resource use for each woman. Maternal antenatal and postnatal hospital admissions and admissions to neonatal care were similar in the two groups. As regards mode of birth, when comparing the groups, the PA group had more assisted and spontaneous vaginal births and the control group had more caesarean sections and miscarriages. A chi-squared test, including all four modes of birth, showed a significant difference between the groups (χ^2=8.7, p<0.035). On average the PA group attended 5.3 of 14 treatments sessions offered, and the control attended 3.5 of 6 sessions offered. The total duration of treatment sessions was around twice that for the PA group compared with the control group.

The point estimate results shown in Table 20 suggest that the PA intervention is somewhat less costly than the control, by a margin of £35 per participant, but produces a small increase in the expected number of quitters. Taken in isolation, this suggests that PA should be adopted, regardless of the decision maker's willingness to pay for an additional quitter. However, this result must be interpreted with great caution because there is considerable statistical uncertainty, as reflected in the scatterplot (see Figure 5), which shows that neither cost difference nor effect difference is statistically significant, as there are an appreciable number of points in each quadrant. This is confirmed by the cost-effectiveness acceptability curve (see Figure 6), which shows that the proportion of bootstrapping replications deemed cost-effective does not exceed 80% for any willingness to pay up to £50,000 per additional quitter.

Table 19. Health care service utilisation

	Physical Activity (n=391)	**Control (n=393)**
Maternal antenatal hospital admissions	**N (%)**	**N (%)**
Missing data	46/391 (11.8)	56/393 (14.2)
Admissions	85/345 (24.6)	72/337 (21.4)
	Mean (SD)	**Mean (SD)**
Average length of days per admission[a]	2.9 (10.5)	2.3 (2.5)
Baby admitted to neonatal unit	**N (%)**	**N (%)**
Missing data	31/391 (7.9)	35/393 (8.9)
Admissions[a]	29/360 (8.1)	36/358 (10.1)
Maternal postnatal hospital admissions	**N (%)**	**N (%)**
Missing data	36/391 (9.2)	42/393 (10.7)
Admissions	275/355 (77.5)	271/351 (77.2)
Average length of days per admission[a]	2.1 (1.6)	2.2 (1.9)
Mode of birth	**N (%)**	**N (%)**
Missing data	20/391 (5.1)	22/393 (5.6)
Assisted vaginal birth[b]	49/391 (12.5)	33/393 (8.4)
Caesarean section	77/391 (19.7)	104/393 (26.5)
Spontaneous vaginal birth	239/391 (61.1)	224/393 (57.0)
Miscarriage	6/391 (1.5)	10/393 (2.5)
	Mean (SD)	**Mean (SD)**
Number of treatment sessions	5.3 (4.1)	3.5 (1.9)
Total duration of treatment sessions (mins)	177.3 (146.0)	86.8 (51.2)
Number of sessions using treadmill	4.9 (4.0)	NA
Total time on treadmill (mins)	93.3 (92.2)	NA
Number of crèche sessions[c]	0.46	0.22

[a]The average length of stay is shown for maternal admissions, where a unit cost per day has been applied. For neonatal admissions the unit cost is per admission, so length of stay is not needed. [b]For three sets of twins the first baby had a spontaneous birth and the second had an assisted birth. In these cases the resource use for the mother was counted as assisted. [c]A creche was available at only four of 13 hospital sites and the mean has been calculated across all patients, therefore in this case reporting the SD is not relevant.

Table 20. Results of the incremental cost effectiveness analysis

Intervention costs	Average per-participant Costs (£ in 2012/13 prices)	
Physical activity group	£83	
Control group	£56	
Difference	£27	
Resource use costs	Average per-participant Costs (£ in 2012/13 prices)	
Physical activity group	£4630	
Control group	£4692	
Difference	-£62	
Total costs and outcomes	Average per-participant Costs (£ in 2012/13 prices)	Quit rate
Physical activity group	£4713	7.7%
Control group	£4748	6.4%
Difference	−£35	1.3%
	Expected annual Costs[a] (£ in 2012/13 prices)	Expected annual quitters[a]
Physical activity group	£273,343	4.45
Control group	£275,373	3.69
Difference	−£2029	0.76
Incremental cost effectiveness ratio (ICER)	Not calculated: physical activity dominates the comparator in the point estimate result	

[a]Expected annual costs and number of quitters based on 58 participants per year.

The "stripey" effect in the cost-effectiveness scatterplot (*see Figure 5*) reflects the discrete nature of the outcome measure. One additional quitter selected in the bootstrapping moves the point to the next stripe. It appears that the estimated cost saving from the PA intervention is driven by the increased use of health care resources in the control group, particularly as regards the rate of caesarean section.

Figure 5. Cost effectiveness scatterplot

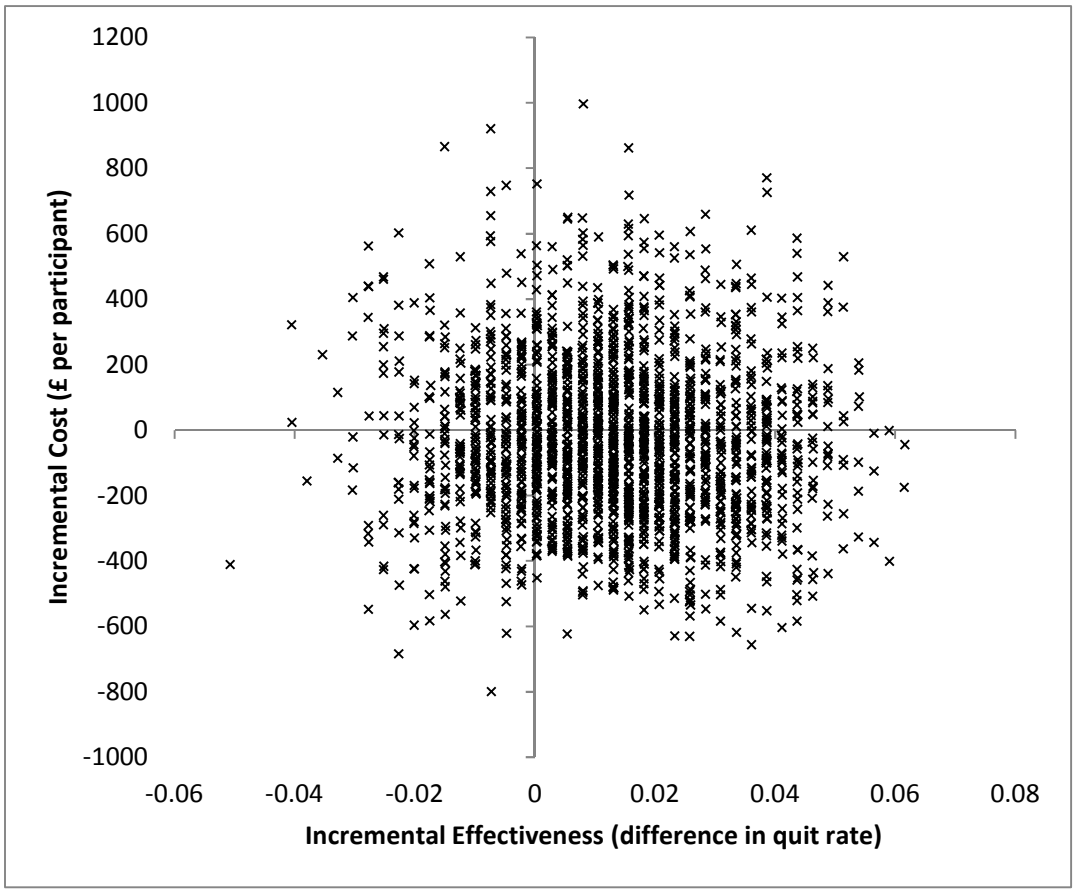
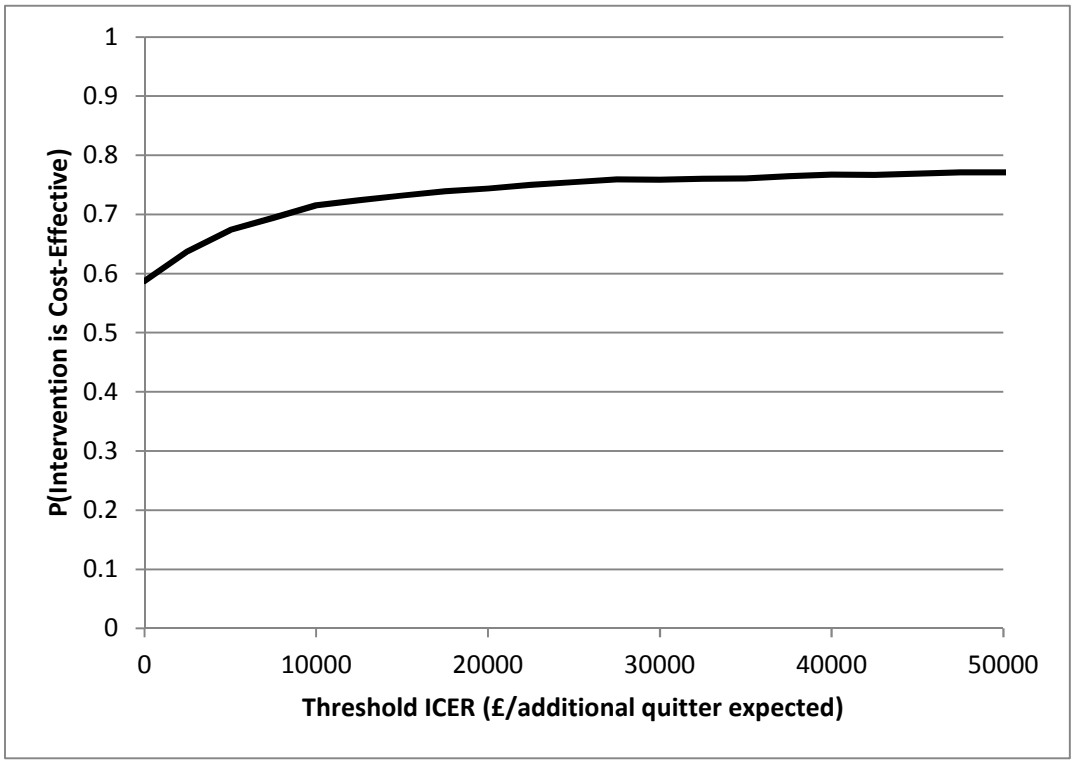


Figure 6. Cost-effectiveness acceptability curve



The results were calculated assuming that the costs for treadmill and midwife training would be based on a typical hospital size. The effect of these costs is negligible compared with other costs in the analysis, and so varying this assumption makes no appreciable difference to the results. *Table 21* presents illustrative results showing the effect on overall costs and difference in costs of two possible scenarios. The first was to halve the per-participant fixed costs, assuming that the treadmill and training would apply to twice as many participants (116 per year instead of 58). The second corresponding change in the opposite direction was to double the per-participant costs, assuming that the treadmill and training would apply only to half as many participants (29 per year).

In a subgroup analysis, when repeating the calculations for the two categories of age and FTCD scores, the point estimates no longer show physical activity dominating the control, but the bootstrapped results still occupy all four quadrants of the cost-effectiveness plane thus it cannot be concluded that the intervention is cost-effective (or not) for any of these subgroups. Further details of the subgroup analysis are in *Appendix 9.*

Table 21. Sensitivity analysis for assumption about handling fixed costs

	Average costs per participant (£ in 2012-13 prices)		
	Physical activity	**Control**	**Difference**
Base case	4713	4748	−35
Halve per-participant fixed costs	4711	4747	−36
Double per-participant fixed costs	4716	4749	−33

Summary

Costs associated with the control and PA intervention were compared and the consequences of these alternatives were estimated. The main results of the cost-effectiveness analysis can be summarised as follows:

- Mean costs were £35 per participant lower in the PA group compared with the control group. This results from the fact that mean intervention costs were £27 higher in the PA group than the control group, but healthcare resource use costs were £62 higher in

the control group. An important contributory factor to this result was the difference in rates of caesarean section (25% in control group versus 19.7% in PA group).

- Taken in isolation, the reduction in mean cost and increase in quit rate taken together suggest that PA should be adopted, regardless of the decision maker's willingness to pay for an additional quitter. However, this result must be interpreted with great caution because there is considerably statistical uncertainty, as reflected in the scatterplot and accompanying cost-effectiveness acceptability curve.
- Subgroup analysis was performed by age and dependency score. In each subgroup analysis, there was still considerable uncertainty in both incremental cost and difference in quit rate.

CHAPTER 5: DISCUSSION

Smoking outcomes

The trial showed that, among women who were recruited at 10 to 24 weeks of pregnancy, supplementing behavioural support with a PA intervention was no more effective than behavioural support alone in promoting cessation at end of pregnancy. At this time, self-reported continuous smoking abstinence rates, with biochemical validation, were 1.3% higher among those in the PA group compared with the control group, but this difference was not statistically significant.

Strengths and limitations

This is the first trial to assess the effect of a PA intervention on smoking cessation during pregnancy. Limitations of previous trials of PA interventions for smoking cessation were overcome[22] through offering an intensive PA intervention with support to increase PA as an aid for smoking cessation in addition to supervised exercise sessions, assessing and validating PA in both groups, using a robust outcome of continuous smoking abstinence, and offering a pragmatic intervention which could be readily integrated into routine healthcare in the NHS. This study was approximately twice as large as previous RCTs investigating individually-delivered PA interventions for smoking cessation.[22] Our sample was 91% of the target 866 and the CIs around the OR for the effect of the intervention are compatible with up to a two-fold increase in abstinence at end of pregnancy compared with controls; however, quit rates were lower than anticipated, increasing the imprecision of our estimates; however, the absolute difference between the groups is unlikely to be clinically meaningful. Additionally, we can exclude a clinically meaningful difference between the groups for our 4 week outcomes because the quit rates were higher and confidence intervals narrower.

Our finding of a lack of an effect of a PA intervention on smoking abstinence is consistent with most previous trials of PA for smoking cessation among non-pregnant smokers. However, these trials had low statistical power or had insufficiently intense interventions.[22] One adequately powered trial showed that regular, supervised, vigorous-intensity physical activity (PA) was effective for smoking cessation in women.[23] However, such an intensive intervention is not likely to be clinically suitable or appealing to most pregnant smokers and our finding remains that a pragmatic intervention based focussing on moderate intensity exercise was not effective for aiding smoking cessation during pregnancy.

Secondary outcomes

Cigarette withdrawal symptoms and urges to smokes

Reports of cigarette withdrawal symptoms and urges to smokes are important during smoking cessation as they predict relapse to smoking and pharmaceutical interventions are thought to largely work through reducing these symptoms.[18] There was no evidence of the PA intervention affecting changes in withdrawal symptoms or urges to smoke, rated for the last week, between baseline and one week of abstinence. The ratings for all the withdrawal symptoms were fairly low at baseline (mean score of 2.3, scale 1-5) and there may have been a floor effect for these items. The lack of PA effect on cigarette withdrawal or urges to smoke is inconsistent with studies showing that brief bouts of PA have an acute effect on reducing urges to smoke among non-pregnant smokers[21] and one study has observed this phenomenon among pregnant smokers.[29] However, these studies are with temporarily abstinent smokers and findings from this study are likely to have more clinical relevance. It is possible that among women attempting to stop smoking, bouts of PA have acute beneficial effects on reducing the urge to smoke but these do not translate into benefits that are extending across the week.

Confidence for taking physical activity and stopping smoking

Increased confidence for PA and smoking cessation (i.e. self-efficacy) tends to predict positive changes in these behaviours[100,101] and, if the PA intervention has the potential to aid smoking cessation, we might expect it to increase self-efficacy in both these domains. There was a significant difference in self-efficacy for PA between baseline and one week for the two groups; however, the difference was a modest 0.3 (scale 1-5) and was the result of scores remaining unchanged in the PA group and scores reducing (i.e. reduction in self-efficacy) in the control group. For the study groups, the difference in scores for self-efficacy for smoking cessation between baseline and one week were 0.2 (scale 1-6) and this was not statistically significant. Thus, there was little evidence to show that the intervention was positively influencing these processes.

Birth outcomes

Maternal and fetal birth outcomes were very similar in the two study groups, except there were significantly less deliveries by caesarean section in the PA group than in the control group (difference of 7%). This is a positive finding as caesarean sections are more expensive to the NHS than other modes of delivery and there are complications associated with abdominal surgery. The finding of a lower incidence of caesarean sections in the PA group is consistent with the results of a recent meta-analysis of RCTs showing a significantly lower

risk of caesarean delivery among women undergoing a PA intervention compared with control conditions[102]. Ours is the first study to report this in pregnant smokers.

Adverse events

There were similar numbers of adverse events and serious adverse events in the two study groups and there were only two AEs potential related to the PA intervention. This is reassuring as it suggests that a PA intervention is safe and is unlikely to increase these events in pregnant smokers.

Maternal weight

There was no evidence that randomisation led to reduced weight gain overall or reduced the tendency to gain excessive weight during gestation. Obesity did not modify the association between trial arm and weight gain.

The subsample of the LEAP participants in this study were much more likely to have stopped smoking than those who were not included. This was because abstinent participants had to return for biological confirmation of abstinence and are obviously keen to return to show their success. Weighing participants was then possible. While this is of some concern, it is a much less relevant concern here than it might appear. Post-cessation weight gain occurs only in those who sustain abstinence, obviously, and therefore there is no potential for PA to ameliorate cessation-related weight gain in those not achieving abstinence. Consequently, the Cochrane review of interventions to prevent cessation-related weight gain confines the analysis to only participants who achieve abstinence in the intervention and control arms.

Pregnancy itself is a period when excessive weight gain occurs commonly, as shown in these women where 38% gained excessively. Physical activity might have been expected to ameliorate this, but there was no evidence it did so. The confidence intervals were wide and encompassed modest effects that are clinically relevant. We can therefore conclude only that the PA programme had no large effects on gestational weight gain but may still have important, moderate sized effects, although there is insufficient evidence to assess this.

Maternal depression

The PA intervention was no more effective than standard behavioural support for reducing depression scores at the end of pregnancy or six months after childbirth. Moreover, scores were significantly higher in the PA group than the control group at the end of pregnancy, although the margin of this difference was very small and is unlikely to be clinically important.[103,104] Adverse events were very similar in the two groups so this is unlikely to have affected the outcomes. As for the smoking outcomes, there may have been limited potential to show a difference between the groups as both groups were already active at baseline and

reported maintaining fairly high levels of PA through to the end of pregnancy. That said, the self-reported PA must be treated with caution as the accelerometer data suggests that these reports were overestimated and, among the sample with accelerometer data, levels of activity were similar for the two groups.

Another explanation for the findings relates to the population of interest and the requirements of the study/intervention. Those in the PA group were asked to change two health behaviours simultaneously (i.e. PA and smoking) while also coping with being pregnant, in addition to dealing with the demands of being asked to attend multiple treatment sessions. This might have demoralised these individuals and they may have found this difficult to achieve, resulting in marginally higher depression scores at the end of pregnancy.

In conclusion, while clinical guidelines recommend that pregnant women exercise for mental health benefits[28,60,105] and there is a further recommendation that PA be used to treat and prevent depression among smokers[106], based on the current findings, an intervention which offers supervised exercise combined with consultations to increase PA cannot be recommended for antenatal or postnatal depression in women attempting to quit smoking during pregnancy.

Economic evaluation

The total mean costs were £35 per participant lower in the PA group compared with the control group. This results from the health care resource use costs being £62 higher in the control group than the PA group, while the mean intervention costs were £27 higher in the PA group than the control group. Control group healthcare costs were higher mostly due to the higher rates of caesarean section in this group (25% in control group versus 19.7% in PA group). Considering the reduction in mean cost and increase in quit rate, for the PA versus control intervention, it could be recommended that the PA intervention be used as an aid for smoking cessation regardless of the decision maker's willingness to pay for an additional quitter. However, these results must be interpreted with extreme caution since there is considerably statistical uncertainty, as reflected in the scatterplot and accompanying cost-effectiveness acceptability curve.

Previous studies have investigated the cost-effectiveness of smoking cessation interventions during pregnancy.[90] However, these mainly USA-based studies are limited by not including data for infant outcomes and therefore cannot easily be compared with this study. One previous study (SNAP), based in the UK, has considered infant outcomes, and conducted a similar analysis as used in the present study. SNAP assessed the cost-effectiveness of NRT for smoking cessation.[94] They reported that the total mean costs were

£90.81 higher in the NRT group compared with the usual care group. While bearing in mind the high levels of statistical uncertainty present in both studies, this suggests that the PA intervention may be at least as cost-effective, if not more so, than the NRT intervention.

NICE (2013) recommends that health outcomes should be measured in quality adjusted life years (QALYs) to facilitate comparisons between different health care programmes.[92] Ideally, the value to society of each successful quitter in the LEAP trial would be estimated in QALYs but no method has been found for doing this that can be considered robust and reliable for use with pregnant smokers. QALYs are commonly calculated from generic health-related quality of life tools (e.g. EQ-5D) which may be inappropriate for use in pregnant populations. Quality of life studies using generic measures have demonstrated that changes in quality of life, particularly declining physical functioning and vitality occur over the course of pregnancy.[107] These substantial changes in quality of life may mask any potential short-term quality of life gains from smoking cessation. Moreover, existing models ignore QALY benefits to the fetus and do not take into account maternal morbidity during pregnancy.[90,91,108] It was anticipated that a model and systematic review being developed for another study at the University of Nottingham would be suitable for this purpose but this work has yet to be completed. However, once an appropriate economic model which values smoking in pregnancy is available we will use this to estimate cost effectiveness in QALYs.

Interpretation and generalizability for smoking outcomes

The trial had reasonably broad inclusion and few exclusion criteria and therefore results are likely to be generalisable to most pregnant smokers; although, the women were highly physically active in both groups at baseline. Low attendance may have affected efficacy, with the PA group attending a median of only four (of 14) sessions. Low attendance was not explained by the two potentially treatment-related adverse events in the PA group and there was no indication that the PA intervention increased the overall incidence of adverse events. The vast majority of women who failed in their quit attempt stopped attending, suggesting that it was failure of quitting that led to low attendance rather than low attendance leading to failure of the attempt. There was no evidence for the intervention influencing processes that might aid cessation, such as confidence for quitting, urges to smoke or withdrawal symptoms.

Bias in outcome ascertainment is unlikely to explain the findings as follow-up rates were equally high in the groups and the effect size was independent of the influence of missing outcome data. Less than 10% reported using non-study behavioural support or NRT, with similar usage in the groups. Therefore, it is doubtful that this influenced the results.

Whilst the intervention group reported significantly higher PA levels throughout pregnancy, relative to the control group, the self-reported PA scores in the control group were also relatively high at follow-up. For example, at end of pregnancy the intervention group reported completing a median of 155 mins of moderate to vigorous intensity PA per week (22 mins per day) and the control group reported 140 mins (20 mins per day). This suggests that some intervention contamination might have occurred in the control group and consequently there was an insufficient difference in PA levels between the groups to show an appreciable effect on depression outcomes. It is not clear why the control group participated in more PA than might be expected. One explanation could be that an atypical motivated sample were recruited who were keen to be active regardless of their random group allocation; the high baseline PA scores would suggest this explanation is a possibility as participants were already achieving around 30 minutes per day of moderate-vigorous PA at baseline. The only previous trial of exercise for smoking cessation showing a long-term benefit for abstinence excluded more active women[23] and in less active women the LEAP intervention might have had more positive effects. However, there was no evidence to suggest that the treatment effect, for the primary outcome, was influenced by baseline levels of physical activity. Moreover, as participants were recruited from routine healthcare settings, it seems likely that similarly active women would be recruited to an exercise intervention delivered as part of routine care.

It is also important to consider that, as previously observed,[109] our accelerometer correlational analysis and Bland-Altman plot suggest that participants overestimated their self-reported PA. Moreover, participants could not be blinded to treatment allocation and the higher self-reported rates of activity in the PA group may be biased by knowledge of treatment allocation. Also, in the sub-sample using the accelerometer, accelerometer-derived PA levels were similar in the two trial groups. The accelerometer data was collected for only 10% of participants and therefore this finding must be treated with caution; however, it is possible that the non-significant effects for smoking abstinence emerged partly because the PA group failed to adhere fully to the behavioural goals of the intervention. If this is the case, then it is unlikely than such an intervention offered in routine health care would raise PA levels sufficiently to have an impact on smoking cessation. On the other hand, although attendance at treatment sessions was low, the PA counselling may have increased PA even without attendance at all scheduled exercise sessions.

Conclusion

During pregnancy, offering an intervention combining supervised exercise and PA counselling did not add to the effectiveness of behavioural support for smoking cessation. There was no evidence that the PA intervention increased AEs or had a harmful effect on birth outcomes and there was some evidence that the PA intervention resulted in less caesarean sections. There was no evidence for the intervention reducing maternal depression or weight gain.

Recommendations for research (in priority order)

1. It is not recommended to fund further large scale trials of PA for smoking cessation until much less expensive observational studies have been conducted to provide promising leads.
2. Reasons for pregnant smokers' low levels of attendance at supervised PA sessions should be investigated; findings could be used to increase attendance rates.
3. Further methods of increasing PA adherence among pregnant smokers need to be developed and tested. For example, financial incentives have shown some benefit for aiding smoking cessation in this population and they may be used in combination with PA to increase both attendance at exercise sessions and smoking cessation. Also interventions are needed which provide regular prompts to remind women to exercise (e.g. text messages, or brief phone calls).
4. The reasons why few sedentary pregnant smokers were attracted to a PA trial need to be identified and methods are needed to attract these less active pregnant smokers.
5. Studies are needed to establish whether the, previously reported, finding of a short bout of PA reducing cigarette cravings in pregnant smokers is a robust finding. So far, only one study has investigated this issue. If it is a robust finding, interventions need to be developed which can translate this benefit into prevention of smoking relapse.
6. There was no evidence of beneficial effects on maternal weight gain or depression. Studies are need which focus on women who are at risk of higher maternal weight gain and on women who have high levels of depression at baseline.

Implications for health care

There was no evidence that offering regular supervised exercise and PA consultations, in addition to routine smoking cessation support, to women following their first antenatal visit is effective for aiding cessation. Therefore, PA is not currently recommended for smoking cessation during pregnancy. One study showed that PA acutely reduces cigarette cravings in abstinent pregnant smokers[29] and, among smokers in general, PA is recommended for

reducing these cravings.[21,22] In the present study there was no evidence for the PA intervention moderating cravings/urges to smoke, but it is possible that there are some acute benefits of PA on reducing cravings during pregnancy, and the recommendation to use PA to manage cravings acutely remains for all smokers, including those who are pregnant. The PA did not show any benefit for reducing maternal depression, in fact there was a slight increase in depression in the PA group; therefore the intervention cannot be recommended for antenatal or postnatal depression in women attempting to quit smoking during pregnancy. There was no evidence for an effect on maternal weight gain, therefore the intervention cannot be currently recommended for moderating this weight gain. There was no evidence of increased adverse events in the PA group and there was some evidence for a reduced incidence of caesarean sections; therefore, in line with current guidance, PA remains indicated for general health benefits in pregnancy, including among pregnant smokers.

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Contribution of authors

All authors made substantial contributions to conception and design and/or to acquisition of data and/or to analysis and interpretation of data as listed below. All authors were involved in drafting the manuscript or revising it critically for important intellectual content. All authors approved the final version.

Michael Ussher (LEAP Trial Chief Investigator/Trial Manager, Professor of Behavioural Medicine) was involved in design, conduct, acquisition of data, analysis and report writing phases.

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Pelham Barton (Reader in Mathematical Modelling) was involved in the design, conduct, analysis and report writing phases specifically for the economic analysis.

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Holly Essex (Research Fellow in Health Economics) was involved in the design, analysis and report writing phases specifically for the economic analysis.

Dale Esliger (Senior Lecturer in the Measurement of Physical Activity) was involved in the design, conduct, analysis and report writing phases specifically for accelerometer data.

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Publications

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APPENDIX 1 : LEAP TRIAL PROTOCOL

(To read the full article, click on the page below)

Ussher et al. Trials 2012, 13:186
http://www.trialsjournal.com/content/13/1/186

STUDY PROTOCOL Open Access

Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial

Michael Ussher[1*], Paul Aveyard[2], Isaac Manyonda[1], Sarah Lewis[3], Robert West[4], Beth Lewis[5], Bess Marcus[6], Adrian H Taylor[7], Pelham Barton[8] and Tim Coleman[9]

Abstract

Background: Many women try to stop smoking in pregnancy but fail. One difficulty is that there is insufficient evidence that medications for smoking cessation are effective and safe in pregnancy and thus many women prefer to avoid these. Physical activity (PA) interventions may assist cessation; however, trials examining these interventions have been too small to detect or exclude plausible beneficial effects. The London Exercise And Pregnant smokers (LEAP) trial is investigating whether a PA intervention is effective and cost-effective when used for smoking cessation by pregnant women, and will be the largest study of its kind to date.

Methods/design: The LEAP study is a pragmatic, multi-center, two-arm, randomized, controlled trial that will target pregnant women who smoke at least one cigarette a day (and at least five cigarettes a day before pregnancy), and are between 10 and 24 weeks pregnant. Eligible patients are individually randomized to either usual care (that is, behavioral support for smoking cessation) or usual care plus a intervention (entailing supervised exercise on a treadmill plus PA consultations). The primary outcome of the trial is self-reported and biochemically validated continuous abstinence from smoking between a specified quit date and the end of pregnancy. The secondary outcomes, measured at 1 and 4 weeks after the quit date, and at the end of pregnancy and 6 months after childbirth, are PA levels, depression, self-confidence, and cigarette withdrawal symptoms. Smoking status will also be self-reported at 6 months after childbirth. In addition, perinatal measures will be collected, including antenatal complications, duration of labor, mode of delivery, and birth and placental weight. Outcomes will be analyzed on an intention-to-treat basis, and logistic regression models used to compare treatment effects on the primary outcome.

Discussion: This trial will assess whether a PA intervention is effective when used for smoking cessation during pregnancy.

Trial registration: ISRCTN48600846

Keywords: Smoking cessation, Pregnancy, Physical activity, Intervention, Randomized controlled trial

Background

Maternal smoking during pregnancy is the major preventable cause of poor health outcomes for women and their babies. Smoking during pregnancy causes substantial harm to mothers and infants, increasing the risks of post-natal depression, miscarriage, stillbirth, prematurity, low birth weight, perinatal mortality and morbidity, asthma, attention deficit disorder, learning difficulties, and obesity [1-6]. Smoking also presents immediate risks for the mother, including placental abruption [7], as well as the longer-term risks reported for smokers in general. Smoking in pregnancy is a major public health problem in high-income countries; in the USA, 14% of pregnant women smoke throughout their pregnancy [8]; in the UK, 12% of pregnant women smoke [9], although a figure of 40% has been reported in deprived areas [10].

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APPENDIX 2: TELEPHONE SCREENING SHEET

Please add site ID no. ☐

To be completed by Researcher by phone:

Researcher's name:	
Date:	Time:
Potential participant's Name:	
Address: Email:……. Daytime tel:…….. Evening tel:…….. Mobile:…… Best time to call is between…… and…… Post Code: No. calls made:…….	
GP's Name: Address: Tel:	
Introduction: Name/role, hospital, research study, spare a few minutes to discuss. **Describe study:** • Help with stop smoking. • Compare usual help/advice with usual help/advice plus exercise. • Around 900 women, several hospitals • Either once a week for six weeks or twice a week for six weeks then once a week for two weeks. 50:50 chance of either group. • Quit one week after first appointment. • Follow-ups at around 38 weeks pregnant, baby six months (at home if preferred) • Questionnaires and CO monitor • £7 travel expenses	

Eligibility Checklist:	**Inclusion criteria**	
1. How old are you?	Age 16 – 50	
2. How many weeks pregnant are you?	10-24 weeks	
3. How many cigarettes did you smoke on a typical day before you were pregnant?	≥ 5 cigs	
4. How many cigarettes do you smoke on a typical day now?	≥ 1 cigs	
5. Are you willing to try to stop smoking without using nicotine replacement therapy (e.g. patches)?	YES	
6. Can you read and write in English?	YES	
7. Are you available and willing to attend up to 14 appointments over the next 2 months?	YES	
8. Do you have a drug or alcohol problem?	NO	
9. Are you able to walk continuously for at least 15 minutes?	YES	
10. Have you been advised by a doctor, midwife or another health professional not to take exercise during your pregnancy?	YES	NO
11. Has a doctor ever said you have a heart condition and recommended only medically supervised physical activity?	YES	NO
12. Do you have chest pain brought on by physical activity?	YES	NO
13. Have you developed chest pain in the last month?	YES	NO
14. Do you tend to lose consciousness or fall over as a result of dizziness?	YES	NO
5. Do you have any bone or joint problems that become aggravated when you are more active?	YES	NO

16. Has a doctor ever recommended medication for your blood pressure or a heart condition?		YES	NO
17. Are you aware, through your own experience or a doctor's advice, of any other medical reason why you shouldn't be physically active without medical supervision?		YES	NO
18.If woman answers YES to any of Q10-17: Do I have your permission to contact a doctor at your hospital to check if it is ok for you to exercise? <u>If woman answers no:</u> She cannot take part.		YES	NO
If yes to Q10-17: Consultant has confirmed that it is safe for woman to take part?	NA	YES	NO
<u>For all women who are eligible:</u> Do I have your permission to contact your GP, midwife and obstetrician to let them know you are interested in taking part?		YES	NO
Sent letter to GP about participation?		YES	
Suitable for trial?		YES	NO
Information sheet & directions sent?		YES	

Date of first appointment:	Time: Clinic:

Remind the women to bring a pair of shoes comfortable for walking in, in case she is in the exercise group.

APPENDIX 3: THERAPIST MANUAL FOR DELIVERING BEHAVIOURAL SUPPORT FOR SMOKING CESSATION

Smoking cessation support manual for LEAP trial

This manual includes guidance all 43 behaviour change techniques (BCTs), except BM4 "Provide rewards contingent on successfully stopping smoking", defined in the following taxonomy:
Michie S, Hyder N, Walia A, West R (2011) Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. Addictive Behaviour, 36, 315-9. The 43 BCTs used are:

Specific focus on the target behavior (*B*) and maximizing motivation (*M*): BM1. Provide information on consequences of smoking and smoking cessation; BM2. Boost motivation and self-efficacy; BM3. Provide feedback on current behavior; BM5. Provide normative information about others' behavior and experiences; BM6. Prompt commitment from the client there and then; BM7. Provide rewards contingent on effort or progress; BM8. Strengthen ex-smoker identity; BM9. Identify reasons for wanting and not wanting to stop smoking; BM10. Explain the importance of abrupt cessation; BM11. Measure CO. **Maximizing self-regulatory capacity and skill (*BS*)**: BS1. Facilitate barrier identification and problem solving; BS2. Facilitate relapse prevention and coping; BS3. Facilitate action planning/develop treatment plan; BS4. Facilitate goal setting; BS5. Prompt review of goals; BS6. Prompt self-recording, BS7. Advise on changing routine; BS8. Advise on environmental restructuring; BS9. Set graded tasks; BS10. Advise on conserving mental resources; BS11. Advise on avoiding social cues for smoking. **Promoting adjuvant activities (*A*)**: A1. Advise on stop-smoking medication; A2. Advise on/facilitate use of social support; A3. Adopt appropriate local procedures to enable clients to obtain free medication; A4. Ask about experiences of stop-smoking medication that the smoker is using; A5. Give options for additional and later support. **General aspects of interaction focusing on delivery of the intervention (*RD*)**: RD1. Tailor interactions appropriately; RD2. Emphasize choice; **General aspects of interaction focusing on information gathering** (RI): RI1 Assess current and past smoking behaviour; RI2. Assess current readiness and ability to quit; RI3. Assess past history of quit attempts; RI4. Assess withdrawal symptoms; General aspects of interaction focusing on general communication (RC): RC1. Build general rapport; RC2. Elicit and answer questions; RC3. Explain the purpose of CO monitoring; RC4. Explain expectations regarding treatment program; RC5. Offer/direct toward appropriate written materials; RC6. Provide information on withdrawal symptoms; RC7. Use reflective listening; RC8. Elicit client views; RC9. Summarize information/confirm client decisions; RC10. Provide reassurance.

The specific BCTs used are indicated in brackets in the manual below. The version of the manual used by therapists did not include these BCT labels.

Each smoking cessation consultation should take about 20 minutes.

Session 1: Preparation for quitting

Briefly describe the study and intervention and check volunteer's understanding:

- **Explain randomisation** e.g. 'A computer will decide whether you will get the standard treatment or the exercise programme. Do not be too concerned about which you are getting. Whatever you receive, you are in with a good chance of succeeding in stopping smoking. In both conditions we shall be providing help and support to help you to stay free of smoking.'
- **Remind them what the interventions will involve (RC4)** e.g. 'If you are in the exercise group you will need to attend 14 appointments over 8 weeks. This will involve waking on a treadmill for up to 30 mins and advice and support with stopping smoking and taking regular exercise. If you receive the standard treatment you will be asked to attend 6 weekly appointments providing advice and support with stopping smoking.
- **Explain the timing of the target quit date** (TQD): We will ask you to stop smoking one week from today. **(BS4)**
- The volunteer should not be randomised using the online database until you are satisfied that she understands what the study will entail (especially the need to attend all appointments) and understands the process of randomisation.

IF RANDOMIZED:

- **Explain the purpose of carbon monoxide (CO) monitoring (RC3)**
- **Measure CO (BM11) and use the reading to motivate quitting.**
  e.g. 'This shows how much you inhale the smoke and all the dangerous chemicals in it. A non-smoker would normally have a reading of less than eight. You as a smoker have a reading of ___. As soon as you stop smoking, this will start to go down to the non-smoking level. This will happen not just in your own body, but in the body of your baby as well. There is an immediate health benefit in stopping smoking. We shall repeat this measure once a week.'

- **Briefly discuss reasons for wanting to quit, level of motivation for quitting and confidence for quitting** (refer to questions in CRF) **(BM9, R12)**
- Assess and discuss current and past smoking behavior (see questions in CRF) (**RI1**)
- **Discuss past attempts at quitting (R13)** and reasons for relapse. Determine longest periods of abstinence and, if these are reasonably lengthy, use these as a reason to be optimistic to about being able to quit.
- **Discuss preparing for the quit day (BM6, BS3)**; e.g. "I suggest you make a list of the things you need to do to prepare for your quit day. For example: Tell people you are quitting, particularly those who will give you support **(A2)**, decide when you will have your last cigarette, tell people that they will not be allowed to smoke in the home, remove all ashtrays and from your home **(BS8)**, become aware of times when you are most likely to lapse (e.g. after meals, when alone in the house, on phone) and make a note of these **(BS6)**, think about how you will deal with these times and be aware that one puff can easily turn into a full relapse **(BS1)**." Also ask them to think about whether there are any events coming up that might make it difficult not to smoke (e.g., a stressful event or party, or meeting someone they used to smoke with) **(BS1)**. Mention that there will be more time to discuss these strategies on their quit day.
- **Discuss whether partner smokes** and whether partner or friends or colleagues might want to quit with them. Invite partner to join them at their treatment sessions. **(A2)**

- **If they have children**: discuss what they will do with children during the sessions. Also, suggest they explain to the children that they are quitting and that they ask the children to encourage them. **(A2)**
- Explain clearly that the woman can have the last cigarette before the session on their quit day (e.g. outside the clinic before coming in, on the morning or the night before their quit day. No smoking after that) **(BS4)**. If they can, ask them to decide now when they would like to have their last cigarette and say that it is their choice **(RD2).**
- **Give a leaflet about smoking and smoking cessation during pregnancy (BM1, RC5)**
- If they ask **whether they should start cutting down** in preparation for quitting, explain that it is better not to start missing cigarettes before the real quit attempt begins. This is likely to be a better way to quit than having long breaks between the last few cigarettes, enjoying them greatly, and saying 'goodbye ciggies' with tears in their eyes and having strong cravings before they have even quit.
- **If volunteer says they are content with cutting down to 2 or 3**, consider mentioning the following to encourage them to quit abruptly and completely **(BM10)**
- It is often anxiety and discomfort that motivates behaviour change rather than logic:

Encouraging Women to Quit Completely
Not much benefit to be had by cutting down as you inhale more deeply and more nicotine reaches the baby. You have the worst of both worlds as you are experiencing the discomfort of cutting down and doing the same harm to yourself and the baby.
You will be adding more stress making those few cigarettes more precious and there is also the stress of withdrawal between those few cigarettes. Better to quit completely.
It is best to quit completely now because the pressure that comes with having a new baby will make it more likely that you will relapse.

- If they ask about **self-rolled and low tar cigarettes** explain that these are just as harmful. **(BM1)**

Session 2: Quit Day

Objectives

- Remind patient that today is their quit day
  Look for reasons why woman is a good prospect (BM3) (e.g. managed to quit for a period of time in the past, she is highly motivated, lessons learned from previous attempts, success/change in other areas of their life, is receiving best available support etc.). Express your optimism. Make it clear that they need to be prepared for it being very difficult (particularly if quitting was difficult in the past, CO is high and/or they smoke their first cigarette soon after waking), but that many women in their position quit successfully

- **Stress the importance of a good start**. e.g. 'You have shown determination by getting as far as this. Now is the crunch time. Even if the first few days prove to be difficult, do not go back to smoking. As a long-term smoker, you need to expect at least some difficult moments. The good news is that there is strong evidence that making it through the first week without a single puff massively increases your chances of success. Please remember this when you are tempted to smoke.
- **Explain the withdrawal symptoms** that they may experience. 'Besides cravings, many people feel irritable, depressed, restless, have poor concentration, sleep disturbance and feel hungrier.' Also some people get more colds, mouth ulcers and headaches. **(RC6).** Reassure that these will gradually decrease across the first 3-4 weeks of quitting. The first week often is the hardest and the middle of the first week is often the worst time.
- **Smoking and stress:** Explain that smoke increases rather than reduces stress and that most people feel less stress within a week or two of quitting.
- **If they are ambivalent about quitting** remind them of why they want to quit.
- **Discuss possible obstacles to success and briefly review coping strategies** for week ahead: Ask 'What happened when you tried to stop smoking before? Refer woman to tips in the leaflets. Ask "Are there any particular events this week that might increase your temptation to smoke?" **(BS1)**

  Explain that cravings often only last a few minutes and that they tend to peak and then subside. Recommend that they prepare for these cravings **(RC6)** (e.g. distract yourself, have an activity ready, for exercise group suggest a short walk, have someone you can call when you are close to lapsing, keep healthy snacks in your bag (e.g. apples, carrot sticks) and water (some people say that sipping helps with cravings), have things to keep your hands occupied, avoid/minimize difficult/stressful/tempting situations if you can (e.g. parties, time spent with smokers,), especially in the first few weeks **(BS11)**. If they cannot avoid these situations suggest they be prepared for it to be a challenge. Explain that it can also be useful to change their daily routine (e.g. if they usually smoke first thing in the morning suggest they replace this with something else, such as a shower or breakfast). **(BS7)** Suggest that they also conserve their energy, particularly in the first few weeks, by not taking on major new projects such as making other significant changes in their life **(BS10)**.

- A typical tempting situation which may lead to smoking is when people are bored with not much to do. If this affects you, make plans for distracting yourself. To give you an example, Mrs. Palmer found that for her, making a jigsaw helped. She started a jig-saw puzzle on her quit day and when tempted to smoke went and looked for the next piece of her jigsaw.

- **Suggest cognitive strategies (RC6)** . Some people benefit from 'talking themselves through' difficult situations; e.g. remind yourself that the difficult moment will soon pass, remember your reasons for stopping smoking and the danger of having even one slip, think of all you've achieved so far, think how you will feel if you lapse and have a cigarette, write down all the reasons why you don't want to smoke and keep this with you, keep a picture of the baby's scan with you.
  - 'If tempted to smoke, have a look at the tips in this leaflet. Distract yourself if it gets tough. Take it one day or even one hour at a time. **(BS9)**

  Remember that if you pull through this week without smoking at all, you are far more likely to succeed.

- If they make these preparations this will **build up their resistance** when they are tempted to smoke.
- **Finish by stressing the importance of not having a single puff of a cigarette** as this can quickly lead to having more cigarettes and it will increase your cravings. You may feel that having just one cigarette won't hurt and will make you feel better. Be on your guard! This is how attempts at quitting fail. Do not fool yourself. **(BS2)**

Session three : one week after quit day

Main aims :

- **Assess CO** and give feedback about whether their reading has reduced **(BM11, BM3).**
- **How do I handle discrepancies between CO and self-report?**
  - Best not to challenge self-reports, but check again that client did not smoke
  - Check ambient CO
  - Check your own reading
  - Ask about the possibility of exposure to secondary tobacco smoke.
  - Ask about possibility of exposure to CO at home (e.g. leaky gas boiler)
  - Say that you will calibrate the CO monitor and check their reading again again next week
- **Review** how they got on this week with remaining abstinent and discuss whether the strategies they prepared were helpful. **(BS5)**
- **Boost motivation**, provide orientation on withdrawal, discuss possible reasons for relapse and strategies for dealing with these **(BS2)**.
- **Reinforce abstinence**, deal with lapses.

Check smoking status. If abstinent, praise and reinforce: e.g. **"**If you did not smoke at all, you are now free of nicotine and of many other chemicals in cigarette smoke which are bad news for your baby" (**BM7**).

- **If they lapsed,** explain again the importance of complete cessation, but do not discourage (e.g. 'You still have time to catch up. How do you plan to go about it?'*).* Discuss a plan. Look for a positive angle. Explain to lapsers who complain of withdrawal discomfort that this will only go away if they do not smoke at all – see below. Check for unrealistic expectations ('e.g. Despite the exercise/NRT, I still fancied a cigarette'). **If they have relapsed** back to regular smoking encourage them to learn from why they relapsed and to set a new quit date **(BM6)**. If they have relapsed, discuss whether they would consider using NRT **(RD2)** and provide **advice about NRT (A1)**. Liaise with the PCT to enable them to get free NRT **(A3)**.

- **Discuss withdrawal discomfort** and refer to their responses to the withdrawal questions in the CRF **(R14)**. Reassure where appropriate *(*e.g., 'Over many years, your brain and body have got used to having regular shots of nicotine throughout your waking hours. Once you stop smoking, it can take weeks and months to regain your balance.'*).* Explain the likely duration of concrete symptoms patients are concerned about. Reassure them that most smokers experience strong withdrawal symptoms and that cravings are the most common symptom **(BM5, RC10)**; e.g. "They can be unpleasant, but they will not harm you. You will be over the most difficult time soon". Suggest they continue to be aware of, or make a note of, when they are most tempted to smoke **(BS6)**.
- **Discuss triggers for relapse and coping efforts (BS2)** where appropriate. Encourage them to use: distraction techniques (I go and do something, get away from the situation, etc.), avoiding temptations (I do not have any cigarettes in the house, did not go to the pub this week), and cognitive approaches (I think of my reasons for stopping, tell myself to take one day at a time, I imagine how bad/guilty I will feel if I smoke etc.).
- Suggest they start **seeing themselves as a non-smoker**, rather than as a smoker who is trying to quit or an ex-smoker. If they do this they are more likely to succeed. (e.g. if someone offers them a cigarette suggest they say 'No thanks, I don't smoke', and ask them to imagine saying this) **(BM8)**.
- Allow time at the end of each session for the **participant to ask questions (RC2)**.
- Remind participant that if they attend all six smoking cessation sessions they will be entered into a **prize draw** for three £100 shopping vouchers. **(BM7)**

<u>Sessions 4 (two weeks after quitting) onwards</u>

Main aims:

Reinforce abstinence or deal with lapses.

Give reassurance on withdrawal (at later sessions deal with weight gain).

Discuss obstacles, advise on coping, express support.

Tailor the content for each individual **(RD1)**

- **Check smoking status (BS5).** Congratulate abstainers and praise them. Explore how they got through difficult moments; elicit, reinforce, and develop coping strategies. Note they are now making it (first 2 weeks) or have made it through the most difficult part of quitting.
  If not abstinent, discuss barriers to quitting. Explain the urgency of catching up
- **If a participant is smoking** daily, debrief on difficulties that led to smoking, and suggest lessons learned and future solutions (**BS2**). Help patient decide whether to continue current quit effort or to set a new quit date (**BM6**). Frame the experience positively, and focus on future efforts. Offer to refer them to the PCT for further support during or following the research intervention **(A5)**.
- **Discuss triggers for relapse and coping strategies (BS2)**
- **If you go through a difficult patch**, remember that it will get easier soon. Your brain and body got used to regular doses of nicotine. It can take a few weeks, or more, to get back your balance and to learn to live without smoking. Most people feel OK within some three or four weeks.

- **Ask about use of NRT**: refer to the questions in the CRF and, for those who are using NRT, ask how they are getting on with it. **(A4)**
- **Emphasise the rationale of recommending complete abstinence** and the danger of relapse.
- By now, you have probably **saved quite a bit of money** you would otherwise spend on cigarettes. This saving will grow quickly. Plan how to spend it on yourself.

FU at six weeks after quitting: remember that you **need to conduct a 7 day physical activity recall via telephone for control group 6 weeks after quit.**

- Explain the danger of relapse and the need to stay on guard. 'Many smokers who make it through pregnancy go back to smoking after the birth or within a year of quitting. I would like to make sure that this will not happen to you'. (**BS2**)
- Warn against 'transgression' cigarettes when stressed, when bored, on holidays, and in company. Discuss the temptation people often have 'to try one cigarette, just to see', explain the dangers, especially in the hours and days after the birth. **(BM8, BS2)**
- Discuss likely relapse situations (e.g. smokers they will come in contact with soon after the birth) and plan coping strategies. (**BS2**)
- Emphasise woman's ability to cope and implement cessation procedures on their own, building on the success to date.
- The woman may be concerned about what will happen after the visits finish. In case they need to contact you, give them your clinic phone number. Offer them the option of being referred on to the PCT stop smoking service for further support. Give them information about the NHS website for pregnant smokers (www.smokefree.nhs.uk/smoking-and-pregnancy/) **(RC5)** and the smokefree helpline: 0800 022 4332. **(A5)**
- If they say they feel tempted in the company of smoking friends/family, suggest they consider asking these individuals not to smoke around them, or just plan how to react when one of them lights up or offers a cigarette. (**BS2**)
- "One of these days you will realise that you have not thought of smoking at all for hours. Notice this. It will soon become days and then weeks, until cigarettes will stop being an issue at all."
- "Every day you make it without smoking, you are learning how to cope without cigarettes and finding your own ways to overcome difficult moments. Notice what helps and use it."
- "The link between smoking and everyday activities such as getting up in the morning, speaking on the phone, or having a meal will by now be weakening – notice such positive developments."
- "If you still have difficult moments, do not fall into the trap of thinking that one cigarette will not hurt. Even a puff could put you in serious danger of undermining all you have achieved so far." (**BS2, BM8**)
- "Try to eat a healthy, balanced diet. This includes plenty of fruit and vegetables, and not too much fried and fatty food. Keep a supply of healthy snacks with you. Watch out for high calorie, high fat snacks, but do not go hungry."

Tips for preventing relapse (BS2)

If you have not smoked at all, or very little, for over four weeks now, you are really getting there. Once the regular support is over, here are some tips to prevent you going back to smoking:

- Think ahead of situations which could be dangerous for you. Boredom? Stress? Getting drunk? Wanting to enjoy yourself? Think now how you are going to cope. When the situation comes, remember how you prepared for it.
- Do not think that after being a non-smoker for a few months, one cigarette will not make any difference. It will be as dangerous as ever.
- Even if things are still difficult on occasions, sooner or later, you will lose interest in smoking, or even start to dislike the very idea of it. You are very close now to join millions of others who have stopped smoking for good.

Some women who quit smoking successfully when pregnant start to smoke again after they give birth. Stay on your guard.

- Passive smoking is harmful for your baby.
- Quitting smoking is very difficult. You have now done the hard part. It would be a shame to spoil it all.
- Sooner or later you will start thinking of yourself as a non-smoker and the idea of smoking will start to look rather strange and less appealing.

Notes on the support process (this also applies to physical activity counselling)

Key things to remember:

- **Summarise** information the women needs to remember **(RC9)**.
- **Reflective listening**: reflecting back to the women what they are saying, particularly the emotional content (e.g. I can appreciate that it makes you angry and frustrated to see your partner continuing to smoke around the house when you have quit). **(RC7)**
- **Acknowledge their fantasies** about smoking, but explain why they are unrealistic (e.g. Yes, I can see that you would love to have the occasional cigarette, but smokers who do this very quickly start smoking on a daily basis back to their original levels of smoking). In general, try and explore their views on smoking cessation (**RC8**).
- **Descriptive praise**: describe what they are specifically doing well at and praising them for this (e.g. you did well to throw all your cigarettes away because I know you partly wanted to keep some for an emergency), rather than just using general praise (e.g. you are doing very well). **(BM4)**
- **Preparing for success**: Focus on helping the women to plan so that things go right (e.g. preparing for triggers to smoking), rather than having to 'react' when things go wrong **(BS1)**.
- **Maintaining a positive tone** e.g. avoid criticism, use pleasant tone of voice and body language, focus on solutions rather than problems, keep your sense of humour! **(RC1)**

For those familiar with psychological counselling, it is important to note that brief smoking cessation support is much more directive and goal-oriented than general counselling approaches.

APPENDIX 4: THERAPIST MANUAL FOR DELIVERING PHYSICAL ACTIVITY INTERVENTION

Physical Activity Intervention Manual

(refer also to participant's handbook)

This manual includes guidance on 19 of 40 behaviour change techniques (BCTs) defined in the following taxonomy: Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP (2011) A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychological Health, 2, 1479-98.
The 19 BCTs covered in this manual are: 1. Provide information on consequences of behaviour in general; 2. Provide information on consequences of behaviour to the individual; 7. Action planning; 8. Barrier identification/problem solving; 9. Set graded tasks; 10. Prompt review of behavioural goals; 12. Prompt rewards contingent on effort or progress towards behaviour; 13. Provide rewards contingent on successful behaviour; 16. Prompt self-monitoring of behaviour; 20. Provide information on where and when to perform the behaviour; 21. Provide instruction on how to perform the behaviour, 22. Model/Demonstrate the behaviour; 23. Teach to use prompts/cues; 26. Prompt practice; 27. Use of follow-up prompts; 29. Plan social support/social change; 34. Prompt use of imagery; 35. Relapse prevention/coping planning; 38. Time management.

The specific BCTs used are indicated in brackets in the manual below. The version of the manual used by therapists did not include these BCT labels.

Each consultation should take about 20 minutes.

Session 1 (one week before quit date)

- **Review her current PA levels** (refer to seven day recall of physical activity).
- **Explain how to use treadmill (BCT 21:** Instruction on how to perform behaviour**)**

- Explain warm-up (3mins walking, hold stretches for 10 secs for front thighs, calves, hamstrings and reach overhead for upper body) and warm down (slow down for final minute of walking, repeat stretches)
- Recommend rating of perceived exertion of 12-14 and show RPE chart. Explain about 'Talk Test', and that exercise should be intense enough for her to be breathing heavier than normal
- Demonstrate use of treadmill (**BCT 22**: Demonstrate behaviour)
- Ask women to walk on treadmill for 15-30 mins
- Agree how long she will walk (it is fine if she exceeds this goal, as long as it is no more than 30 mins)

- **Discuss benefits of exercise (BCT 1:** Provide information on consequences of behaviour in general**)**

- Mention that regular exercise has been shown to reduce cravings in a similar way to nicotine replacement.
- Mention that exercise is also good for a healthy pregnancy. Say that there will be more time to discuss these benefits at the next session.

● **Agree PA goals for this week (BCT 7:** Action planning**)** for exercise she will do outside the treadmill Sessions:
- Recommend she starts with at least one session of 15 mins PA.
- Recommend that she gradually progresses towards 30 mins of PA on 3 to 5 days a week (plus treadmill sessions).
- Agree a SMART goal, e.g. 'I will walk for 20 mins around the park at lunchtime, on 5 days this week'.

● **Explain how to use pedometer**
- Ask her to wear pedometer for the rest of today and to take it off last thing at night and then to open it and record the number of steps in the diary.
- Each morning, ask her to put pedometer on as soon as she gets up and to wear it all day. Again, taking it off last thing at night and recording the number of steps (**BCT 26**: Prompt practice). Say that she can keep the pedometer.

● **Ask her to complete PA and steps diary** for everyday this week (**BCT 16**: Self-monitoring of behaviour). Write her PA goal for this week on the top of the diary.

Session 2 (few days before quit day)

● **Review goals/plans**
- Check whether she has managed to do any PA in her own time since the last session
- Briefly review woman's goals for taking PA in her own time for week ahead (**BCT 10:** review of behavioural)
- Check she has been able to use the pedometer OK and is recording her daily steps. If she is averaging less than 10,000 steps a day recommend a 10% increase in her current steps over the next two weeks (**BCT 7:** action planning, **BCT 9:** set graded tasks).

● **Go though physical activity booklet with woman**
- Ask her to write down what she sees as the main benefits and disadvantages (if any) of becoming more active during her pregnancy and remind her of other benefits (**BCT 2**: Consequences of behaviour to the individual).
- Testing times: ask her to write down any barriers that might prevent her from achieving her PA goal and think of ways of overcoming these barriers (**BCT 8:** Barrier identification problem solving).
- Go though the tips for exercising in the booklet and praise her for any specific adjustments she has made to her lifestyle to encourage exercise (**BCT 12**: Rewards contingent on effort or behaviour). Suggest that she rewards herself when she achieves her exercise goals (e.g. a special meal at the end of the week) (**BCT 13**: Reward contingent on successful behaviour).
- Demonstrate the home exercises in the booklet and ask her to try each of the level 1 exercises/stretches with you. **(BCT 21:** Instruction on how to perform behaviour, **BCT 22**: Demonstrate behaviour). Encourage her to practice the exercises at least once before the next meeting (**BCT 26**: prompt practice). When she is confident with the level 1 exercise, go through the Level 2 exercises/stretches at a future session.
- Provide information on local opportunities for exercise (e.g. walking schemes, antenatal exercise classes) (**BCT 20:** information on where and when to exercise).
- Encourage her to exercise at regular times (e.g. a walk after lunch) so that it becomes a habit (**BCT 23:** Teach to use prompts/cues). If she has raised lack of time as a barrier to exercise, suggest she manages her time to fit in exercise by timetabling exercise slots into her week (**BCT 38**: time management).
- Suggest she tries to find people who will exercise/walk with her (**BCT 29**: Plan social support).

● **Ask woman to walk on treadmill for 15-30 mins**

- If she walked for less than 30 mins at the last session recommend that she walks for 5 mins longer this time and at each further session, until she is walking continuously for 30 mins.
- Agree how long she will walk for.
- After exercise: Remind woman to complete PA and steps diary every day this week.

Session 3 (quit day)

● Briefly review physical activity the women has done in her own time and adjust goals for physical activity in general and for pedometer (**BCT 10:** review of behavioural goals)

● Discuss any barriers that might prevent her from achieving her PA goal and think of ways of overcoming these barriers (**BCT 8:** Barrier identification problem solving).

- Praise her for any specific adjustments she has made to her lifestyle to encourage exercise (**BCT 12**: Rewards contingent on effort or behaviour). Discuss how she is rewarding herself when she achieves her exercise goals (**BCT 13**: Reward contingent on successful behaviour).

● Set heart-rate zone and ask woman to wear HR monitor while on treadmill:

HEART RATE TARGETS/(training zone):

Less active (ie reporting less than 150 mins PA in the last week), overweight (BMI=25 – 29.9) or obese (BMI=30+) women:
Start with light intensity heart-rate range:
Aged 16-29: 102 -124 bpm
30 years plus: 101-120 bpm

Gradually progress to moderate intensity HR range:
Aged 16 -29: 125 -144 bpm
30 years plus: 121-144 bpm

Active women (ie reporting at least 150 mins/week):
Moderate intensity HR range:
Aged 16-29 145-160 bpm
Aged 30 plus 140-156 bpm

● Ask woman to walk on treadmill for 15-30 mins

● Ask woman to check that she keeps her heart rate in the training zone, and ask her to maintain her walking at a level where she is still able to hold a conversation

● Give exercise diary and ask her to fill it in each day this week.

Consultation Session 4 (one week after quit day) onwards

● Review physical activity the women has done in her own time:

- Discuss barriers that may prevent her maintaining and increasing her physical activity and how she might deal with these (**BCT 35**: relapse prevention/planning)
- Agree plans for PA for the coming week:
- Refer back to physical activity booklet if necessary

● Praise her for any specific adjustments she has made to her lifestyle to encourage exercise (**BCT 12**: Rewards contingent on effort or behaviour). Discuss how she is rewarding herself when she achieves her exercise goals (**BCT 13**: Reward contingent on successful behaviour).

● Review whether she has found people who will exercise/walk with her.

- Review exercises in booklet.
- Ask woman to walk on treadmill for 15-30 mins
- Ask her to imagine herself becoming fitter and healthier and to imagine herself walking briskly with energy and with lungs free of tobacco (**BCT 34**: use of imagery)
- Remind her that for the last two weeks of the exercise programme you will see her once a week rather than twice a week (**BCT 27**: use of follow-up prompts).

Notes on the support process

Key things to remember:

- **Summarise** information the women needs to remember
- **Reflective listening**: reflecting back to the women what they are saying, particularly the emotional content (e.g. I can appreciate that it is very difficult to find the time to exercise).
- **Descriptive praise**: describe what they are specifically doing well at and praising them for this (e.g. you did well to buy some new trainers; this shows that you are serious about taking more physical activity), rather than just using general praise (e.g. you are doing very well).
- **Preparing for success**: Focus on helping the women to plan so that things go right (e.g. preparing for when it rains), rather than having to 'react'.
- **Maintaining a positive tone** e.g. avoid criticism, use pleasant tone of voice and body language, focus on solutions rather than problems, keep your sense of humour!

APPENDIX 5: PARTICIPANT PHYSICAL ACTIVITY BOOKLET

LEAP

Name:……

Guide to physical activity during your pregnancy

BENEFITS

Regular physical activity during your pregnancy has many benefits for you and your baby; such as:

- Less varicose veins, leg cramps and swelling of the legs
- Better posture, balance and muscle tone
- Reduced constipation and back ache
- Easier and shorter labour, in many women
- Better mood, sleep and energy
- Less tobacco withdrawal symptoms (such as feeling irritable) and cravings, and an increased chance of becoming a non-smoker

Write down what you feel are the main benefits and disadvantages for you of becoming more active during your pregnancy:

BENEFITS	DISADVANTAGES

- Can you think of any way of overcoming the disadvantages?

- If you think of any more benefits add them to the list.

Set a realistic goal each week for how much activity you can manage each day

MY GOAL:

- Aim to gradually build up to 30 minutes of activity each day.

TESTING TIMES

- Write down anything that might stop you from achieving this goal
- Try and think of what you can do when this happens

Why I might miss a day's exercise	What I can do when this happens

SOME TIPS

1. Don't smoke, walk!
When you feel a strong craving for a cigarette try going for a brisk walk, even if it is only for 5 minutes. Soon you will start feeling like a non-smoker.

2. Make it Fun
● Choose activities which you enjoy, and which fit easily into your day. Try walking part of the way to or from work or the shops. How about swimming
or following your home exercise routine?
● Play music while you're exercising.
● Involve friends or family.

3. Do it every day
● Gradually increase the number of days on which you are active.
● Then increase the time you are active for each day.
● Gradually build up to 30 minutes of physical activity each day.

4. Make it a habit
● Exercise at the same times each day, so that it becomes a habit.
● Try starting the day with a few gentle exercises or going for a walk.

5. Take it easy
● Choose activities that make you breathe slightly harder than normal, but are not hard enough to stop you having a conversation.
● Do just a little more (10-20 minutes extra) each week.
● Give your body time to adjust to being pregnant and to being without cigarettes.

6. Reward yourself
● Each extra day that you are a non-smoker and have reached your exercise goal give yourself a treat.
● Give yourself an extra treat at the end of each week; something like a special meal.

7. Plan ahead
Plan ahead for interruptions such as bad weather - an ideal opportunity to try your home exercise routine!

8. Keep a diary
Keep a daily record of how many minutes exercise you do and how many steps you do. It will help you to see your progress.

LOOK AFTER YOURSELF!

1. When to avoid exercise

- If you feel unwell, extremely tired or have just eaten a meal.
- In very hot or very humid conditions.

2. When to stop exercising

Stop exercising immediately if you feel any dizziness, nausea, severe pain or tiredness, extreme breathlessness or cold sweats.

3. Breathe Freely

- Keep breathing freely whilst you are exercising.
- To ease breathing: stop and lift your arms up and out.

4. Drink plenty of water Before, during and after exercise.

5. Have a healthy snack soon after exercising, such as a banana.

6. Avoid exercising on your back.

- During the middle and later stages of your pregnancy exercising on your back can cause discomfort.
- It may also reduce your blood pressure for a short time.

7. Pace yourself

Start slowly and gradually work up to a pace where you are breathing slightly heavier than normal, but not gasping for breath.

HOME EXERCISE PROGRAMME

1. **Build up gradually**
   - For each exercise aim for a number of repetitions which you can handle comfortably
   - Aim to gradually build up the number of repetitions you do, until you can do 20 or more
   - If you want to exercise for longer you can gradually build up to two or more complete circuits of all the exercises
2. **Taking breaks**
   - At first you may made need a short break between exercises
   - Gradually reduce the length of the breaks, so that eventually you do the exercises continuously
3. **To avoid aggravation or injury:**
   - Start slowly. Give your body time to warm-up
   - Avoid locking your knees when you are standing
   - Keep good posture, with a straight back.
   - Finish by doing some stretches.
4. **Moving up a level**
   Start with the exercises at level 1. When you are comfortable with level 1 move on to level 2.

If you exercise at home, as opposed to in a class, you can choose <u>when</u>, <u>how</u> and at <u>what</u> pace you exercise! Alternatively, you may prefer to <u>exercise in a class,</u> in which case you should inform the teacher that you are pregnant.

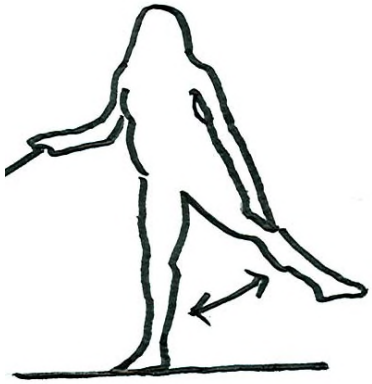
LEVEL 1 EXERCISES

- Try starting with 5 repetitions of each exercise. Over several weeks,
  gradually build to 20 repetitions

- Do at least 10 minutes of exercise by going through all the exercises several times

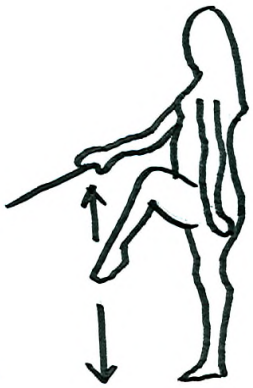
1. Side arm raise

2. Raise on toes

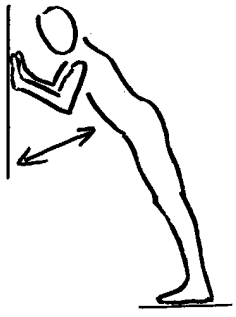


3. Side leg raise

4. Front arm raise



5. Knee raise

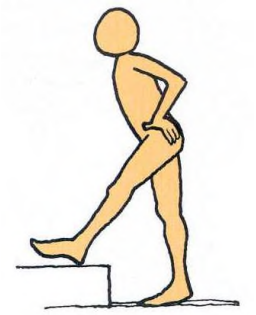


6. Wall-push up

LEVEL 1 STRETCHES

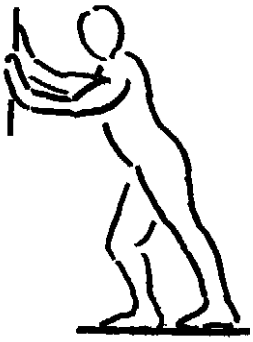
- Stretch regularly to help you feel loose and relaxed. Stretching also will help you with your posture and balance during pregnancy
- Stretch when you are warm, after you have done your other exercises
- Hold the stretch so that you feel a pleasant stretch, do not force the stretch. Avoid any bouncing movements.

1. Pull heel to buttock.
(for front of thigh)



2. Lean over straight leg
(for back of thigh)

3. Reach arms overhead.
(for arms and sides of body)



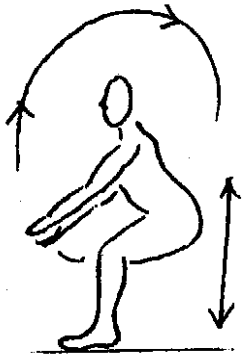
4. Lean on wall, straighten back leg.
(for calves)

Hold each stretch for 10 seconds

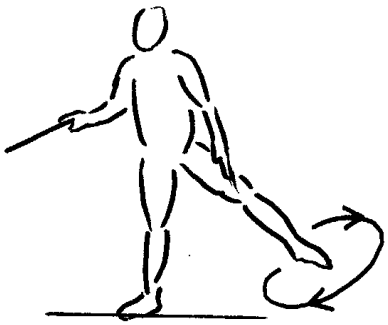
LEVEL 2 EXERCISES

Here are some slightly harder exercises for you to gradually build in

1. Side arm raise + toe raise

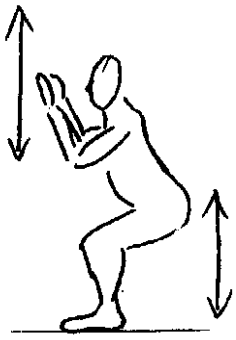


2. Backwards arm circle + leg bend

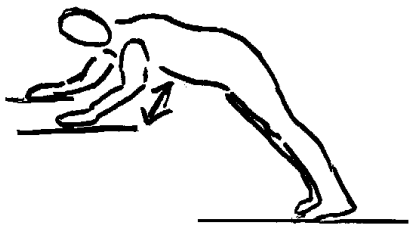


3. Leg circle

4. Front arm raise + knee raise



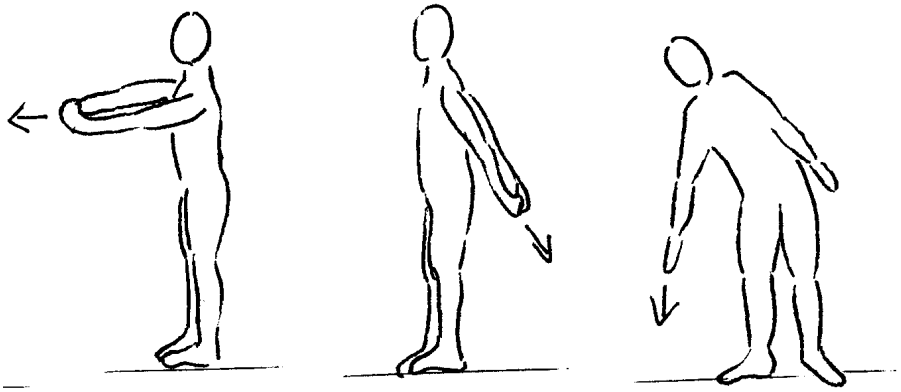
5. Overhead-arm reach + leg bend



6. Push-up on chair

LEVEL 2 STRETCHES

Here are some extra stretches



1. Pull arms forward (upper back & shoulders)

2. Pull arms back (chest & shoulders)

3. Bend to side (waist)

5. Press down on inner thighs (inner thighs)

Hold each stretch for 10 seconds

APPENDIX 6. QUESTIONNAIRES

(*all questionnaires were presented on an online server*)

APPENDIX 6A: BASELINE QUESTIONNAIRE

Participant enrolment details

ID No:

Briefly describe the study and intervention and check volunteer's understanding:	
If they are still willing to participate ask them to sign the consent form and request a randomisation code:	

Participant's date of birth:	
Participant's initials:	
Ethnicity **(see below)**	
NHS number:	
Hospital no:	
Expected date of delivery:	/ /
Midwife's name:	
Midwife's telephone numbers:	Work Mobile
Name and role of person giving intervention at enrolment:	
If research midwife, are you case loading the participant?	Yes/no
Please enter the visit date:	/ /

How would you describe your ethnic group? (*Please check one box only*)	**White**		**Mixed**	**Asian or Asian British**	
	British	1☐	White & Black Caribbean 4☐	Indian	8☐
	Irish	2☐	White and Black African		
	Other	3☐	White & Asian		
			Other Mixed		

	Black or Black British	**Chinese or Other Ethnic Group**
	Black Caribbean	12☐
	Black African	13☐
	Other Black	14☐
Before you became pregnant how many cigarettes did you usually smoke each day?		
How many cigarettes do you usually smoke each day now?		
Did you smoke in a previous pregnancy?	Yes ☐1 No ☐0 Not applicable ☐2	
How soon after you wake up do you smoke your first cigarette?	Within 5 minutes ☐ 3 6-30 minutes ☐ 2 31-60 minutes ☐ 1 After 60 minutes ☐ 0	
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes ☐ 1 No ☐ 0	
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes ☐ 1 No ☐ 0	
Which cigarette would you hate to give up the most?	The first one in the morning ☐ 1 Any other ☐ 0	
Do you smoke even if you are so ill that you are in bed most of the day?	Yes ☐ 1 No ☐ 0	
If you have a partner, does your partner smoke tobacco?	Yes ☐1 No ☐0 Not applicable ☐2	

Confidence for quitting

How high would you rate your chances of giving up smoking, at least until your baby is born?					
Very low	Low	Not very high	Quite high	Very high	Extremely high
1	2	3	4	5	6

Withdrawal symptoms questionnaire

Please show for each of the items below how you have been feeling over the past week.					
	Not at all	Slightly	Somewhat	Very	Extremely
Restless	1	2	3	4	5
Irritable	1	2	3	4	5
Depressed	1	2	3	4	5
Hungry	1	2	3	4	5
Poor concentration	1	2	3	4	5
Poor sleep at night	1	2	3	4	5
Anxious	1	2	3	4	5

Urges to smoke

How much of the time have you felt the urge to smoke in the past week?					
All the time	Almost all the time	A lot of the time	Some of the time	A little of the time	Not at all
5	4	3	2	1	0

How strong have the urges been?					
Extremely strong	Very strong	Strong	Moderate	Slight	No urges
5	4	3	2	1	0

Pregnancy history and demographics

How old are you?	_____ years
How many weeks pregnant are you?	_____ weeks
How many previous pregnancies have you had that have gone beyond 24 weeks?	_____

How many births have you had that were between 24 and 37 weeks of pregnancy?	
How many children are in your household?	
Of these how many are you the biological mother of?	
Are you the biological mother of children in any other household?	Yes ☐ 1 No ☐ 0
If yes, how many?	
Are you….	Married or Living with a partner ☐1 Single/divorced/separated/widowed ☐0
How old were you when you left full time education?	or tick ☐ if still in FT education
What is your usual occupation?	☐ No usual occupation

Use of Alcohol

How often do you currently have a drink containing alcohol?				
Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week

How many drinks containing alcohol do you have on a typical day when you are drinking? *(a drink is equivalent to a glass of wine, 1 spirit, or half pint beer)*				
1 or 2	3 or 4	5 or 6	7 to 9	10 or more

Feelings questionnaire (EPDS)

We would like to know how you are feeling. Please check the box that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you are feeling today.

1. I have been able to laugh and see the funny side of things.

0☐ As much as I always could

1☐ Not quite so much now

2☐ Definitely not

3☐ Not at all

2. I have looked forward with enjoyment to things.

0☐ As much as I ever did

1☐ Rather less than I used to

2☐ Definitely less than I used to

3☐ Hardly at all

3. I have blamed myself unnecessarily when things went wrong.

3☐ Yes, most of the time

2☐ Yes, some of the time

1☐ Not very often

0☐ No, never

4. I have been anxious or worried for no good reason.

0☐ No, not at all

1☐ Hardly ever

2☐ Yes, sometimes

3☐ Yes, very often

5. I have felt scared or panicky for no very good reason.

3☐ Yes, quite a lot

2☐ Yes, sometimes

1☐ No, not much

0☐ No, not at all

6. Things have been getting on top of me.

3☐ Yes, most of the time I haven't been able to cope at all

2☐ Yes, sometimes I haven't been coping as well as usual

1☐ No, most of the time I have coped quite well

0☐No, I have been coping as well as ever
7. I have been so unhappy that I have had difficulty sleeping. 3☐Yes, most of the time 2☐Yes, sometimes 1☐Not very often 0☐No, not at all
8. I have felt sad or miserable. 3☐Yes, most of the time 2☐Yes, quite often 1☐Not very often 0☐No, not at all
9. I have been so unhappy that I have been crying. 3☐Yes, most of the time 2☐Yes, quite often 1☐Only occasionally 0☐No, never
10. The thought of harming myself has occurred to me 3☐Yes, quite often 2☐Sometimes 1☐Hardly ever 0☐Never

Physical activity, height, weight and CO reading

How confident are you that you will be able to do thirty minutes of physical activity (e.g. take a regular walk) on at least 5 days of the week during your pregnancy?

Not at all confident	Slightly confident	Moderately confident	Very confident	Extremely confident
1	2	3	4	5

What effect do you think being physically active (e.g. a brisk walk) will have on your success at quitting?

Large negative effect	Moderate negative effect	Slight negative effect	No effect	Slight positive effect	Moderate positive effect	Large positive effect
-3	-2	-1	0	+1	+2	+3

Maternal height (cm)	
Maternal weight (kg) as measured at booking appointment	or tick ☐ if unknown
Maternal weight (kg) as measured at this visit	

Exhaled Carbon Monoxide (CO) reading	ppm

Have you conducted an interview of seven day recall of physical activity?	☐ tick
Record total number of minutes of physical activity in the previous week	minutes

Record the main type of physical activity (*check one box only*):

☐ Walk
☐ Structured home exercise
☐ Structured exercise at a facility
☐ Housework
☐ Swimming
☐ Do it yourself
☐ Cycling
☐ Gardening
☐ Dancing
☐ Sport/individual
☐ Sport Team
☐ Occupational
☐ Other

Smoking quit date, exercise and smoking desire

Treatment session start time:	☐ hh:mm
Inform the participant that they have been allocated to the physical activity group and briefly remind them what this will entail	☐
Agree a quit date	☐
Give leaflet about smoking cessation.	☐
Advise patient to identify situations when they are most likely to smoke, and to think of how they are going to address them.	☐
Physical activity group only:	
Explain how to use treadmill, recommend a Rating of Perceived Exertion (RPE) of 12-14 and explain the talk test:	☐
Agree a target for the number of minutes of treadmill walking for this session.	☐
Ask woman to exercise on treadmill for between 15-30 minutes	☐

Immediately before exercise (*for those in the control group this was asked immediately before the behavioural support*):
How strong is your desire to smoke right now?

Not at All strong			Somewhat strong			Extremely strong
1	2	3	4	5	6	7

Record time walking on treadmill	☐ minutes

Immediately after exercise ask: (*for those in the control group this was asked immediately after the behavioural support*): How strong is your desire to smoke right now?						
Not at All strong			Somewhat strong			Extremely strong
1	2	3	4	5	6	7
Discuss: benefits of exercise & barriers, aim to progress towards a target of at least 30 minutes a day or 10, 000 steps, how to use pedometer					☐	
Give patient activity diary (including steps diary), ask them to fill it in each day this week, and to bring it to the next session.					☐	
Book further appointments and give appointment card					☐	
Give £7 travel expenses and ask them to sign for it					☐	

Treatment session end time:	☐ hh:mm
Length of treatment session	☐ minutes

APPENDIX 6B: ADDITIONAL QUESTIONS ASKED POST-QUIT DAY ONLY

Have you smoked at all since your quit day?			
1. No not even a puff	2. Yes just a few puffs	3. Yes between 1 and 5 cigarettes	4. Yes more than 5 cigarettes
If you have smoked more than 5 cigarettes and have returned to smoking on a daily basis, how many cigarettes are you currently smoking **each day**?			

Have you used any Nicotine Replacement Therapy (NRT) this week?	YES / NO
Which type of NRT have you mainly used?	☐ Not Applicable ☐ Patch ☐ Gum ☐ Inhalator ☐ Lozenge ☐ Tablets ☐ Nasal Spray

How many days approximately have you used NRT in the past week?						
N/A	1 day	2 days	3 days	4 days	5 days	6 days

End of pregnancy behavioural support question:

Besides the help we have given you, have you received any face-to-face support for stop smoking during your pregnancy? Yes/no
If yes, approximately how many sessions have you attended?

APPENDIX 6C. ANTENATAL COMPLICATIONS AND BIRTH OUTCOMES

Woman's age at delivery ☐ years

Number of Births

Has there been multiple births (e.g. twins or triplets)?	Yes/ No
If yes, please state the number of births/infants:	
Maternal death:	Yes/ No
If yes, please state date of death:	*dd-mmm-yyyy*

Antenatal complications

Gestational hypertension/Pregnancy induced hypertension (PIH):	Yes/ No
Pre-eclampsia (PET):	Yes/ No
Intrauterine growth restriction (IUGR):	Yes/ No
Details of IUGR: Date of diagnosis	*dd-mmm-yyyy*

Baby 1 (scan @ 20 weeks)	
Abdominal circumference:	*mm*
Head circumference:	*mm*
Femur length:	*mm*

Baby 2 (scan @ 20 weeks)	
Abdominal circumference:	*mm*
Head circumference:	*mm*
Femur length:	*mm*
Baby 3 (scan @ 20 weeks)	
Abdominal circumference:	*mm*
Head circumference:	*mm*
Femur length:	*mm*

● Antepartum haemorrhage (APH) requiring hospital admission Yes ☐ No ☐

Incident No.	Date (dd/mmm/yyyy)	Gestation Weeks	Days	Duration (Days)	Amount *	Cause of APH**
1						
2						
3						
4						

* Options for AMOUNT:

-Spotting

-Light

** Options for CAUSE of APH:

-Unknown

-Placenta Praevia

• Urinary tract infection (UTI) in pregnancy Yes ☐ No ☐
If yes (UTI), how many? ☐

• Other infection in pregnancy Yes ☐ No ☐

• Oligohydramnios Yes ☐ No ☐

• Polyhydramnios Yes ☐ No ☐

• Congenital malformation Yes ☐ No ☐
If yes, give type of malformation: ☐

• Premature rupture of membranes (PROM)? Yes ☐ No ☐

• Prelabour rupture of membranes? Yes ☐ No ☐

• Number of antenatal day unit (ADU) attendances ☐

Reason(s) for antenatal attendance (tick all that apply):		
☐ Abdominal pain	☐ Growth scan	☐ Severe headaches
☐ Itching	☐ Reduced fetal movement	☐ Vaginal (PV) bleeding not req. admission
☐ Fainting/dizziness	☐ Spontaneous rupture of the membranes (SROM)	☐ Chest pain/shortness of breath
☐ Intramuscular (I/M) iron administration	☐ Generally unwell	☐ Obstetric cholestasis (OC)

☐ External cephalic version (ECV)	☐ Urinary tract infection (UTI)	☐ Anti-D administered
☐ PET screen	☐ Scoliosis	☐ Symphysis pubis dysfunction (pelvic girdle problems)
☐ Cardiotocography (CTG)	☐ Membrane sweep	
☐ Other reasons:		

- Hospital admissions overnight for women to antenatal ward: ☐ nights

Birth outcome data

Labour

● Onset of labour:

- Spontaneous
- Induced
- Augmented
- No labour – Elective c/s (caesarean)
- No labour – Emergency c/s

● Pain relief*: (tick all that were taken)*

- Water
- Tens
- Entonox (Gas & air)
- Opiate
- Epidural
- Spinal
- General anaesthetic (GA)
- General anaesthetic (GA) following failed epidural/spinal
- Combined spinal-epidural (CSE)

● Mode of delivery:

- Spontaneous vaginal delivery (SVD)
- Assisted vaginal breech
- Ventouse
- Forceps
- Elective c/s (caesarean)
- Emergency c/s
- Semi-elective c/s (i.e. elective brought forward as an emergency)

1 .

2.

3.

● Reason for c/s:

- Not applicable
- Not available

- Previous c/s
- Failed induction of labour (IOL)
- Fetal distress
- Failure to progress
- Placenta praevia
- Antepartum haemorrhage (APH)
- Failed instrumental
- Poor obstetric history
- Failed external cephalic version (ECV)
- Macrosomia
- Pre-eclampsia (PET)
- Obstetric cholestasis (OC)
- Multiple pregnancies
- Abdominal Cerclage
- Breech
- Fetal abnormality
- Previous 3rd or 4th degree tear
- Placental abruption
- Unstable lie
- Maternal medical condition
- Maternal request/tocophobia
- Suspected scar dehiscence
- Uterine rupture
- Cervical fibroid covering internal os
- Previous gynae. surgery
- Cord prolapse
- Severe symphysis pubis dysfunction (pelvic girdle problems)
- History of back injuries
- Orthopaedic complication restricting induction
- Cephalopelvic disproportion

● Duration of 1st stage of labour ☐ minutes

● Duration of 2nd stage of labour ☐ minutes

● Duration of 3rd stage of labour ☐ minutes

☐ ☐

• Total duration of labour hours minutes

Duration of ruptured membranes:	
	☐ *weeks* ☐ *days* ☐ *hours*

• Blood loss at delivery ☐ mls ☐ estimated ☐ measured ☐ both

Outcomes for infant

If birth did not take place**:**

• Maternal death Yes ☐ date ☐

dd-mm-yyyy

• Fetal outcome:

- *Alive* *Baby 1.* ☐
- *Fetal death In utero <24 weeks* *Baby 2.* ☐
- *Fetal death In utero >24 weeks* *Baby 3.* ☐
- *Intrapartum death (i.e. at delivery)*
- *Neonatal death* ☐

• Date of delivery of baby (dd/mm/yyyy)

• Time of delivery of baby ☐ : ☐ (hh:mm)

• Gestational age at delivery ☐ + ☐ (weeks + days)

• Age of mother at delivery ☐ (years)

• Number of fetuses ☐

• Baby(ies) sex

1. Male
   Female

2. Male
   Female

3. Male
   Female

• Baby(ies) birth weight

1 . ☐ grammes

2. ☐ grammes

3. ☐ grammes

• Customised birth weight centile
(to be calculated using desktop programme)

1 . ☐

2. ☐

3. ☐

• Placental weight ☐ grammes Unknown ☐

• Baby(ies) head circumference 1. ☐ mm 2. ☐ mm 3. ☐ mm

• Baby(ies) length 1. ☐ mm 2. ☐ mm 3. ☐ mm

• 1 minute Apgar score 1. ☐ 2. ☐ 3. ☐

• 5 minute Apgar score 1. ☐ 2. ☐ 3. ☐

• Resuscitation:

1. Yes ☐ No ☐

2. Yes ☐ No ☐

3. Yes ☐ No ☐

• Baby(ies) cord pH - arterial:

1. ☐

2. ☐

(Record information for twins, but cord pH not recorded for multiple births.)

• Baby(ies) cord pH - venous:

1. ☐

2. ☐

• Admission to neonatal intensive care unit (NICU)/special care baby unit (SCBU)

Yes ☐ No ☐

• Hospital admissions overnight for women to postnatal ward ☐ nights

• Total nights admitted to hospital ☐ nights

(calculated by totalling antenatal nights (see page 3.) and postnatal nights in hospital)

● Feeding at hospital discharge:

Infant 1

- Exclusively breastfed
- Mixed feeding
- Exclusively infant formula

Infant 2

Exclusively breastfed

- Mixed feeding
- Exclusively infant formula

Infant 3

Exclusively breastfed

- Mixed feeding
- Exclusively infant formula

APPENDIX 7: STATISTICAL ANALYSIS PLAN

Version no. 1.0

Date: 7th November 2012

Full trial title: A pragmatic randomised controlled trial of physical activity as an aid to smoking cessation during pregnancy

Acronym: London Exercise And Pregnant smokers (SNAP) trial

International Standardised Randomised Controlled trial Number: ISRCTN48600346

Trial sponsor: St George's University of London

Chief investigator: Professor Michael Ussher

Analysis Plan prepared by: Professor Michael Ussher, Professor Sarah Lewis,

Nominated statisticians for analysis: Professor Sarah Lewis, Professor Michael Ussher, Muhammad Riaz

Projected start date: 1st April 2009

Recruitment to be completed: end of Nov 2012

Expected completion date: July 2013 (primary endpoints)

Published Trial protocol: Ussher et al (2012) Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial. Trials, 13(1):186.

1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1 Objectives and aims

The LEAP trial will investigate whether or not a physical activity intervention plus behavioural support is more effective than behavioural support alone (control) in achieving smoking cessation at 'end of pregnancy' for women who are between 10 and 24 weeks pregnant, who currently smoke 1 or more cigarettes daily and who smoked 5 or more cigarettes daily before pregnancy. We will also determine the cost-effectiveness of the intervention.

1.2 Trial configuration: Multicentre, parallel group with 1:1 allocation between physical activity and control.

1.3 Randomisation procedures

1.3.1 Points of randomisation and the baseline visit

After confirming eligibility, informed consent for trial entry is sought. After consenting to trial entry, women are randomised. Randomisation is via the Nottingham Trials Unit web-based database and randomisation service. In each centre the recruiting research midwife (RM) has a username and password. She logs on to the trial website that hosts the trial database confirms that the patient eligibility criteria are all met and enters *registration* data about the participant and centre before randomisation is possible. The computer then issues a trial number, which is a unique identifier for the trial participant, and a treatment allocation code.

1.3.2 Specify block size, whether randomly varied

Random permuted blocks of randomly varying size.

1.3.3 Stratified allocation, or post-stratified analysis

Randomisation is stratified by trial centre only.

1.4 Allocation concealment:

As this is a behavioural intervention, there is no allocation concealment for participants or researchers.

1.5 Stopping rules determined as part of the protocol

Stopping rules have not been specified.

1.6 Outcomes

1.6.1 Primary outcome

The primary outcome is self-reported, continuous abstinence from smoking between the quit date and end of pregnancy, validated by exhaled carbon monoxide (CO) or salivary cotinine.

Continuous abstinence is defined as having smoked less than 5 cigarettes since the quit day.

Exhaled CO: The criteria for confirming abstinence is a reading of <8ppm.

Salivary cotinine: The criteria for confirming abstinence is a value of <10ng/ml.

End of pregnancy: It is acceptable for this measure to be taken at a follow-up up to 4 weeks before birth, at delivery, or within 10 weeks after the birth.

The primary outcome is dichotomous; i.e. abstinent or non-abstinent.

For a participant to be classed as abstinent from smoking at end of pregnancy (i.e. positive primary outcome)**:**

At 4 weeks post-quit (It is acceptable for this measure to be taken between 25 days to 6 weeks post-quit): [a]

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' or 'missing' [a] (i.e. any response other than 'yes, more than 5 cigarettes')

AND CO is <8ppm

AND/OR cotinine is <10ng/ml

OR CO or cotinine is missing[b]

AND

At end of pregnancy:

Have you smoked at all since your quit day?= 'No not even a puff' or 'yes just a few puffs' or 'Yes, between 1 and five cigarettes' (i.e. any response other than '5 or more cigarettes')

AND CO is <8ppm[b]

AND cotinine is <10ng/ml[c]

For a participant to be classed as non-abstinent from smoking at end of pregnancy (i.e. negative primary outcome)**:**

At 4 weeks or end of pregnancy:

- Have you smoked at all since your quit day?= 'yes, more than 5 cigarettes'

- CO or salivary cotinine values do not confirm abstinence.

- Has withdrawn from the study (i.e. refuses follow-up).

- Fails to set a quit date which the follow-up assessment can be referenced against.

At end of pregnancy:

- Refuses to allow biochemical validation

- Refuses to self-report number of cigarettes smoked.

- Unable to contact in order to confirm smoking status (i.e. lost to follow-up).

---

[a]Some women will not have data for self-report of smoking or biochemical validation at 4 weeks. If these women are confirmed as abstinent at end of pregnancy it will be considered as a positive primary outcome. All those classed as abstinent at end of pregnancy will automatically be classed as abstinent at 4 weeks post-quit.

[b]Some participants will only have CO or cotinine and, for these women, a reading in the stated range is defined as a positive primary outcome (even without the reading for the other biochemical measure). Most participants will have both CO and cotinine and, for these women, BOTH readings must fall within the defined ranges to count as a positive outcome.

[c]If a new normative value becomes available during the trial this will be used.

1.6.2 Secondary outcomes

Included in paper reporting primary outcomes:

a) Smoking abstinence

Self-reported, continuous abstinence from smoking (up to 5 cigarettes allowed) between quit date and 4 weeks, with biochemical validation (to compare success rates with NHS standards).

b) Physical activity

1. Self-reports of physical activity levels at 1, 4 and 6 weeks after the quit date and at end of pregnancy. Also, at each time point, the numbers reporting walking as the main physical activity.

2. Record of duration of time on treadmill, during supervised exercise.

3. Accelerometer record (Actigraph) of minutes of at least moderate intensity physical activity, during the first week after the quit date. This data is only for 10% of participants.

4. Among those in the exercise group, record of pedometer steps (among those choosing to wear a pedometer at 1, 2, 3, 4, 5 and 6 weeks after the quit date.

c) Aids to smoking cessation

1. Use of nicotine replacement

2. Use of behavioural support other than that provided in the trial

Included in other papers:

a) Smoking abstinence

1. Self-reported, continuous abstinence from smoking (up to 5 cigarettes allowed) between quit date and 6 months after delivery (no biochemical validation).

2. Among those women who relapse, levels of smoking reduction between baseline and end of pregnancy.

3. Lapse free smoking abstinence between quit date and 4 weeks and end of pregnancy (both biochemically validated) and between quit date and six months (without validation).

b) Physical activity

Self-reports of physical activity levels at six months after the birth

c) Psychological outcomes

1. Weekly urges to smoke at baseline and 1, 2, 3 and four weeks after the quit day.

2. Daily urges to smoke on each day in the first week following the quit day.

3. Desire to smoke before and after supervised exercise weekly up to 4 weeks after the quit day.

4. In control group only: Desire to smoke before and after smoking cessation counselling weekly up to 4 weeks after the quit day.

5. Tobacco withdrawal symptoms at baseline and 1 and 4 weeks after the quit day.

6. Self-confidence in stopping smoking at baseline, 1 and 4 weeks after the quit day, end of pregnancy and 6 months after the birth.

7. Self-confidence for maintaining regular physical activity at baseline, 1 and 4 weeks after the quit day, end of pregnancy and 6 months after the birth.

8. Self-reported depression at end of pregnancy and 6 months after the birth.

d) Maternal weight

Maternal gestational weight at baseline, 4 weeks after the quit day and end of pregnancy. (Some of the end of pregnancy measures may be up to 10 weeks after the birth).

e) Fetal loss and morbidity and other fetal and birth outcomes

The following perinatal measures are extracted from patient's hospital records: (i) antenatal complications, including any admissions and the reasons for the admissions, (ii) gestation at onset/induction of labour (and indication for induction where appropriate), (iii) duration of labour and mode of delivery, (iv) Apgar scores of infants, and where available acid-base status of infants, and rates of transfer to the neonatal intensive care unit, (v) birth weight and placental weight.

1. Miscarriage (non-live birth prior to 24 weeks gestation) and stillbirth (non-live birth at 24 weeks gestation or later)
2. Intrapartum death (i.e. at delivery)
3. Neonatal death (i.e. from live birth to 28 days)
4. Intrauterine growth restriction (IUGR)
5. At 20 week scan, abdominal circumference, head circumference, femur length
6. Oligohydramnios (deficiency of amniotic fluid)
7. Polyhydramnios (excess of amniotic fluid)
8. Congenital malformation (and type of malformation)
9. Individualized birth weight Z score (i.e. birth weight adjust for gestational age, maternal height, maternal weight at booking and ethnic group).
10. Unadjusted birth weight and birth weight as Z-score
11. Apgar score
12. Cord blood pH
13. Gestational age at birth
14. Intraventricular haemorrhage
15. Neonatal enterocolitis
16. Neonatal convulsions
17. Congenital abnormality
18. Neonatal intensive care unit (NICU) admission
19. Infant ventilated > 24 hrs
20. Elective termination
21. Elective termination undertaken for fetal morbidity judged incompatible with fetal / infant survival

f) Maternal morbidity and mortality and other maternal outcomes

1. Maternal mortality
2. Gestational hypertension/Pregnancy induced hypertension (PIH)
3. Pre-eclampsia (PET):
4. Antepartum haemorrhage (APH) requiring hospital admission
5. Urinary tract infection (UTI) in pregnancy (and number of infections)
6. Pre-labour rupture of membranes at pre-term (i.e. before 37 weeks) (PPROM)
7. Pre-labour rupture of membranes at term (i.e. 37 weeks onwards) (PROM)
8. Number of antenatal day unit (ADU) attendances
9. Hospital admissions overnight for women to antenatal ward:
10. Reason/s for antenatal attendance
11. Other antenatal complications
12. Onset of labour (e.g. induced)
13. Pain relief
14. Mode of delivery
15. If caesarean section, reason for CS
16. Duration of three stages of labour and total duration of labour
17. Duration of ruptured membranes
18. Blood loss at delivery
19. Proteinuria

g) Health economic data

1. Duration of maternal hospital admission for childbirth

2. Duration of any admission (of baby) to special care

1.7 Determination of Sample Size

A Cochrane review suggests that approximately 9% of women who are still smoking at the time of their first antenatal visit will stop smoking with usual care through to the end of their pregnancy, and a further 6% will stop as a result of a smoking cessation programme using individual behavioural support. Thus, in our control group we expect a smoking cessation

rate of around 15% at the end of pregnancy. Combining our pilot studies 25% (8/32) of participants in the treatment group sustained continuous smoking abstinence to the end of pregnancy. Therefore in the trial we conservatively estimate an abstinence rate of 23% at end of pregnancy in the treatment group, which would be similar to the effect shown for NRT with non-pregnant smokers [14]. We aim to recruit 433 women to each arm to detect the above absolute difference (8%) in smoking cessation rates between the groups at end of pregnancy with a two-sided significance level of 5% and a power of 83%. This calculation is based on a chi-squared test with Yate's correction.

1.8 Protocol amendments that have statistical implications should be described.

For the follow-up at end of pregnancy the valid period for assessment was originally defined as 38 weeks gestation to two weeks after the birth. This was revised to 36 weeks gestation to 10 weeks after the birth.

2. ANALYSIS CONSIDERATIONS

2.1 Analysis for primary outcome

Initially, we will conduct a descriptive comparison of the baseline characteristics of the two treatment groups. Our primary outcome measure, continuous abstinence from smoking from quit date to end of pregnancy, will be compared between treatment groups using logistic regression, adjusted for recruitment centre only, with statistical significance determined by the likelihood-ratio test and with the estimate of effect given as the odds ratio and 95% confidence interval. Our primary analysis will not adjust for any further variables since effect estimates can be sensitive to decisions concerning what variables to adjust for and how these are specified. Nevertheless, the adjustment for baseline covariates is often advised. First, to correct for any chance imbalances in important prognostic variables following randomisation and secondly, because adjusting for highly important prognostic variables in an RCT can improve the precision of treatment effect estimates even when the outcome measure is binary (Robinson, 1991). Statistical testing for baseline imbalances is not advised and instead key covariates should be selected prior to analysis based on the likely magnitude of the association with the outcome measure. Therefore as a sensitivity analysis treatment effects will be reported adjusting for the following variables in addition to centre:

(i) Nicotine dependence score at baseline (Fagerstrom Test of Cigarette Dependence Score, FTCD)

(ii) Age of finishing full time education (in years), as a proxy for socioeconomic status. For a small number of women still in full time education at the time of enrolment the participant's current age will be used instead of age of finishing education.

(iii) maternal age at baseline

(iv) Depression score at baseline (Edinburgh Post-natal Depression Scale, EPDS)

(v) Partner's smoking status (This was not specified in the published protocol, see section 6, p.8 of this SAP).

If we observe differences between the two groups in use of NRT, or use of behavioural support outside of the intervention sessions, then we will conduct a sensitivity analysis to examine the effect of controlling for any differences between groups in these variables. We will analyse other binary smoking outcomes in a similar way.

2.2 Unit of analysis considerations

For outcome measures relating to smoking cessation the women randomised will represent the unit of analysis. All other outcomes will be related to these women, except those related to the offspring (e.g. birth weight), in which case the offspring will be the unit of analysis instead. A small number of children will be born as multiple births (e.g. twins) and data for these cases will be clustered rather than independent. The primary analysis will be of singleton births and we will carry out a sensitivity analysis, including multiple births allowing for the clustering of outcomes. More specifically:

Outcomes where the offspring is the unit of analysis will comprise singleton births only to allow for the fact that observations will be non-independent and that non-singleton births are likely to have very different birth outcomes in any case. In a subsidiary analysis multiple births will be included and clustering accounted for using an approach previously published (Gates S & Blocklehurst P, 2001). This adapts methodology previously created for use with cluster randomised RCTs, assuming that each women is regarded as the 'cluster' and her number of offspring the cluster size.

2.3 Effect modification and sub-group analyses

For our primary outcome, if the intervention is effective, we will look for effect modification by age at leaving full time education and baseline levels of physical activity. Our multiple logistic regression models will therefore be augmented with appropriate interaction terms. Initially, both age at leaving education and baseline physical activity will be fitted as continuous terms to maximise power when testing for an interaction. If evidence of an interaction is present (taken as a p-value of < 0.05) then further subgroup analyses will dichotomise these variables (at the median) for ease of interpretation. The purpose of these models is to establish whether women with low or high levels of education, or high or low baseline levels of physical activity, could benefit preferentially from a physical activity intervention. If there is evidence of interaction, we will perform subgroup analysis of the efficacy of PA compared with usual care in subgroups defined by levels of age at leaving full-time education and by levels of baseline physical activity.

2.4 Analysis for secondary outcomes (not in main paper)

We will compare secondary outcomes, including urges to smoke, withdrawal symptoms, self-confidence and PA, in the first week of abstinence, and the same variables and maternal gestation weight and depression, over subsequent time points, using mixed effects modelling to allow for repeated measures, with adjustment for centre. To deal with non-normally distributed variables we will use transformations to normality, residual bootstrapping, or dichotomising. Differences between groups in perinatal outcomes, including birth-weight and gestation, mode of delivery and complications, will be analysed by linear or logistic regression, with adjustment for centre.

2.5 Timing of analyses

Baseline data with be complete in November 2012 and the baseline characteristics of the sample will then be analysed using descriptive statistics and the results will be presented in tables.

There will be two further main phases of analyses. The first will be begin around July 2013, once the end of pregnancy follow-ups are complete. The second will be conducted for data at

six months after delivery and this analysis will commence around February 2014. Data collected for secondary outcomes will not be analysed until the trial has ended with respect to the primary outcome measure.

2.6 Analysis populations and missing data conventions

Analysis will be on an intention-to-treat (ITT), that is, including all those women randomised to physical activity or usual care. Participants who, for any reason, have missing outcome data on the primary outcome or any secondary smoking outcomes, will be assumed to have resumed smoking.

We will determine the quantity and distributions of missing data. We will carry out a complete case analysis, and we will compare this with an analysis using multiple imputation to deal with missing values, which assumes data is missing at random, describing any differences in terms of the likely biases in the data. The exception is smoking outcomes, where those with missing data will be assumed to have resumed smoking.

2.7 Protocol Deviations

Failure to attend treatment sessions will not constitute a protocol deviation. The only possible protocol deviation is: Women who choose to withdraw from the trial, and choose not to consent for the use of their data for primary or secondary outcomes.

2.8 Derived variables:

Low birth weight – births of <2500g

Preterm birth – births of < 37 weeks gestation

Post-randomisation fetal death - a composite measure of all fetal deaths after randomisation– ***defined as*** – all [miscarriages + stillbirths + neonatal deaths + elective terminations conducted for fetal abnormalities judged inconsistent with fetal / infant life].

Perinatal deaths (a composite measure of all infant deaths following live births) – ***defined as*** – all [stillbirths + neonatal deaths]

2.9 Treatment Compliance and mediation analysis

We will compare compliance between the PA and control groups in terms of the percentage of treatment sessions attended. If the intervention is effective, we will use mediation analysis to examine whether there is evidence that the change in PA levels is the likely causal factor in determining smoking abstinence. We will examine the association between treatment group and change in PA levels, and the association between level of PA and abstinence. Finally, we will include level of PA in a logistic regression model of the association between treatment group and abstinence, with mediation assessed using MacKinnon's causal steps criteria.

2.10 Software used

We will use STATA version 11.

2.11 Levels of significance

All tests will be two-tailed, using a p value of < 0.05 to indicate statistical significance, and 95% confidence intervals will be calculated.

2.13 Format of electronic files for archiving

Excel and SPSS

3. ANALYSIS OF PARTICIPANT CHARACTERISTICS

3.1. Describe methods used to summarise data.

Continuous data that are approximately normally distributed will be summarised in terms of the mean, standard deviation, median, minimum, maximum and number of observations. Skewed data will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

3.2. Disposition

We will summarise the number of patients screened for entry, excluded prior to randomisation by major reason and overall, the number of patients randomised and the number entering and completing each phase of the study by treatment group and overall. We will use a CONSORT flow chart for this.

3.3. Baseline

We will summarise demographic variables (e.g. age, daily number of cigarettes prior to delivery and currently, gestational age at randomisation, exhaled CO, ethnic group, education, parity, etc) by treatment group.

4. ANALYSIS OF ADVERSE EVENTS

The number of adverse events and serious adverse events will be compared between the two groups. There is unlikely to be sufficient adverse events to warrant these being reported in a table.

5. LIST OF PROPOSED SUMMARY TABLES

The proposed tables to be included in the main publication are presented below. We will also produce a CONSORT flow diagram showing exclusions, enrollment and evaluable participants.

6. Changes to statistical analysis plan relative to published protocol

After further statistical review, we request that the TSC approve the following amendment:

1. 'Partners smoking status' has been consistently related to success at quitting smoking in pregnant women and we proposed adjusting for this variable (see section 2.1 above).

2. Section 2.3 'Effect modification and sub-group analyses' was not specified in the protocol and, if the intervention is effective, we propose including this analysis.

Table 1. Demographic and smoking characteristics

(give ranges for all variables)	Exercise group n= Mean (SD)	Control group n= Mean (SD)
Age (years) (range)		
Age at leaving full-time education		
BMI (kg/m^2)		
Weight (kg)		
Gestational age (weeks)		
Cigarettes smoked daily before pregnancy		
Cigarettes smoked daily at randomization		
FTCD score		
Expired carbon monoxide (ppm)		
EPDS score		
Weekly minutes of PA of at least moderate intensity		
	n/%	n/%
Married or living with partner		
Caucasian†		
Professional/managerial occupation		
Smoked in a previous pregnancy		
Parity§ 0-1 2-3 ≥4		
Previous preterm birth††		
Women with partner who smokes		
High confidence for quitting smoking (rated as very or extremely high)		
Takes alcohol ≥ twice a week		

Consumes ≥3 alcoholic drinks on a drinking day		
EPDS score ≥12		
High confidence for PA (rated as very or extremely confident)		
Positive expectation for benefits of PA for quitting (rated as moderate or large positive effect)		

FTND=Fagerstrom Test of Cigarette Dependence EPDS=Edinburgh Post-natal Depression Scale; PA=Physical Activity; BMI=Body Mass Index

† Race or ethnic group was self-reported. Race was categorized according to standard U.K. Census categories.

§ Parity was defined as the number of previous pregnancies that had progressed beyond 24 weeks.

¶ Data exclude XX women in the PA group and XX in the conytrol group who had no partner.

†† Previous preterm birth was defined as any previous pregnancy that lasted from 24 to 37 weeks.

Table 2. Compliance

	Exercise group n= Mean (SD)	Control group n= Mean (SD)
Time walked on treadmill during supervised exercise Baseline one week post-quit 4 weeks post-quit 6 weeks post-quit		NA
Self-reported weekly minutes of physical activity of at least moderate intensity Baseline one week post-quit 4 weeks post-quit 6 weeks post-quit end of pregnancy		
	n/n %	n/n %
Treatment sessions attended		

Table 3. Primary and secondary abstinence outcomes

Outcome	**Exercise group (N=)** Number (percent)	**Control (N=)** Number (percent)	**Odds Ratio (95% CI) †**	**Adjusted Odds Ratio (95% CI)**
Primary Self-reported continuous abstinence[a] at end of pregnancy[b] with biochemical validation[c]§				
Secondary Self-reported continuous abstinence for 4 weeks after quit day with validation†				

† Odds ratios were adjusted for recruitment center only (as a stratification factor).
‡ Odds ratios were adjusted for center, Fagerstrom Test of Cigarette Dependence score at baseline, partner's smoking status and age at leaving full-time education.
[a]Continuous abstinence is defined as having smoked less than five cigarettes since the quit day.
[b]End of pregnancy is defined as between 36 weeks gestation and 10 weeks after the birth.
[c]Validated by either exhaled carbon monoxide or salivary cotinine.
§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in X of X women (X%) in the physical activity group and in X of X (X%) receiving usual care alone.
†§The biochemical tests did not validate the report of not smoking (i.e., probable false reporting of cessation) in X of X women (X%) in the physical activity group and in X of X (X%) receiving usual care alone.

Appendix 8: Supplementary data on adverse events

Serious Adverse Events

Physical activity group: 12 events: Miscarriage (n = 6), Stillbirth (n = 2), Events resulting in a significant disability or incapacity and/or is life-threatening (n = 4)

Control group: 13 events: Miscarriage (n = 10), Stillbirth (n = 2), Neonatal death (n = 1)

Other less frequent adverse events, which occurred in less than 3% of women or infants and are not logically grouped together

Physical activity group:

Maternal adverse events (105 events): Early labour (n = 13), Fainting/dizziness (n = 9), Nausea or vomiting (n = 8), Symphysis pubis dysfunction (n = 8), Severe headaches (n = 7), Chest pain (n = 6), Obstetric cholestasis (n = 4), Oligohydramnios (n = 6), Generally unwell (n = 6), Deep vein thrombosis (n = 2), Group B streptococcus (n = 3), Pelvic pain (n = 3), Polyhydramnios (n = 3), Vaginal discharge (n = 3), Dermatisis (n = 2), Incompetent cervix (n = 2), Uterine contractions during pregnancy (n = 2), Abnormal antibodies, Abnormal blood flow to placenta, Anaemia, Back pain, Bicornate uterus, Diarrhoea, Graves syndrome, Hind waters rupture, Palpitations, Positive urine toxicology, Postpartum haemorrhage, Pregnancy related tachycardia, Right iliac fossa pain, Sciatica, Supraventricular tachycardia, Thyroid problems, Urinary incontinence, Varicose veins (all n = 1).

Fetal adverse events (14 events): Congenital malformation (n = 10), Abnormal fetal heart rate (n = 1), Fetal kidney problem (n = 1), Unstable lie (n = 2).

Neonatal adverse events (15 events): Premature births at <32 weeks (n = 5), n = 9 Congenital malformations (Exomphalos (n = 2), Talipes (n = 2), Anomalous pulmonary venous drainage, Bilateral cleft lip and palate, Enlarged clitoris, Perimembranneous and muscular venticular septal defect, Small sacral skin tag (all n = 1)), Shoulder dystocia (n = 1).

Control group:

Maternal adverse events (114 events): Generally unwell (n = 11), Symphysis pubis dysfunction (n = 11), Fainting/dizziness (n = 10), Oligohydramnios (n = 10), Early labour (n = 8), Nausea or vomiting (n = 8), Obstetric cholestasis (n = 7), Severe headaches (n = 6), Vaginal discharge (n = 5), Polyhydramnios (n = 4), Thrombocytopenia (n = 2), Back pain (n = 4), Diarrhoea (n = 3), Oedema (n = 3), Epigastric pains (n = 2), Placental insufficiency (n = 2), Bells palsy, Chest pain, Deep vein thrombosis, Epileptic fits, Fever, Group B streptococcus, Irritable bowel syndrome, Leaking pulmonary valve, Pelvic pain, Leg pain, Persistent proteinuria, Rectal bleeding, Renal calculi, Right iliac fossa pain, Scoliosis, Sickle cell anaemia, Uterine contractions during pregnancy, Vaginal pain (all n = 1).

Fetal adverse events (14 events): Congenital malformation (n = 9), Unstable lie (n = 2), Abnormal fetal heart rate, Static growth on scan (< 10th centile), Unprovoked decelerations of fetal heart rate (all n = 1)

Neonatal adverse events (9 events): Premature births at <32 weeks (n = 9), n= 5 Congenital malformations (Chronic lung condition, Extra toe on left foot**,** Gastroschisis, Renal dilatation of both kidneys, Renal tract anomaly (all n = 1)).

APPENDIX 9: RESULTS OF SUBGROUP COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness calculations were repeated using data on subgroups from the data stratified by age, and separately by Fagerström Test of Cigarette Dependence score (FTCD). In each case, the population was divided approximately in half. The groups considered were age under 28, age over 27, FTCD<4, FTCD≥4. In this appendix, the point estimate cost-effectiveness results are shown, followed by the cost-effectiveness scatterplot and cost-effectiveness acceptability curve derived from the same approach of imputation and bootstrapping as was used for the complete data set. These results appear in Tables S1-S4 and Figures S1-S8. Note that in each case there is no dominance relationship in the point estimate results, but there is still considerable uncertainty shown on the cost-effectiveness plane and in the cost-effectiveness acceptability curves. A reasonable interpretation of these results is that there is no strong evidence of a subgroup effect.

Table S1. Results of the incremental cost effectiveness analysis for women under 28

	Expected per-participant Costs (£ in 2012/13 prices)	Expected quit rate
Physical activity group	4472	0.0542
Control group	4757	0.0576
Difference	−286	−0.0034
	Expected annual Costs ***(£ in 2012/13 prices)***	Expected annual quitters
Physical activity group	259,348	3.14
Control group	275,932	3.34
Difference	−16,584	−0.20
incremental cost effectiveness ratio (ICER	£84,000 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay *below* £84,000 per additional quitter. This is because the differences in cost and effectiveness are both negative. However, in context, a more reasonable interpretation is that there is no significant difference between the PA and control group results for either cost or effectiveness.	

Figure S1. Cost-effectiveness scatterplot (women under 28)

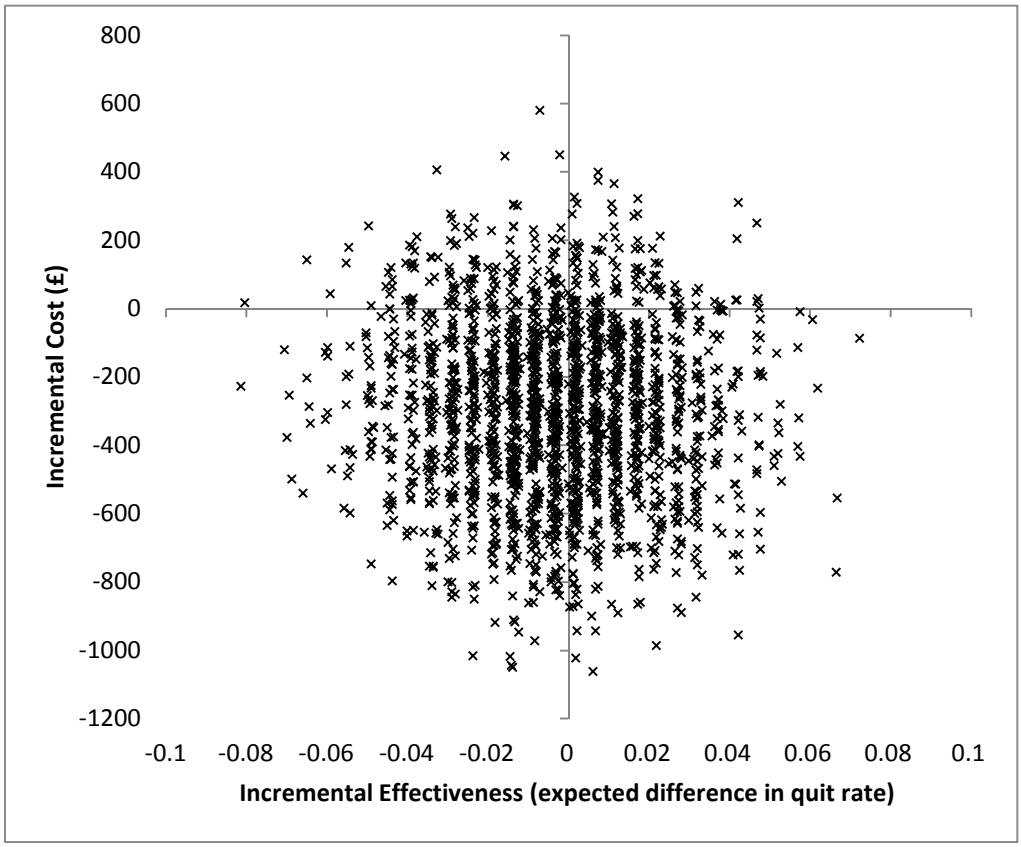


Figure S2. Cost-effectiveness acceptability curve (women under 28)

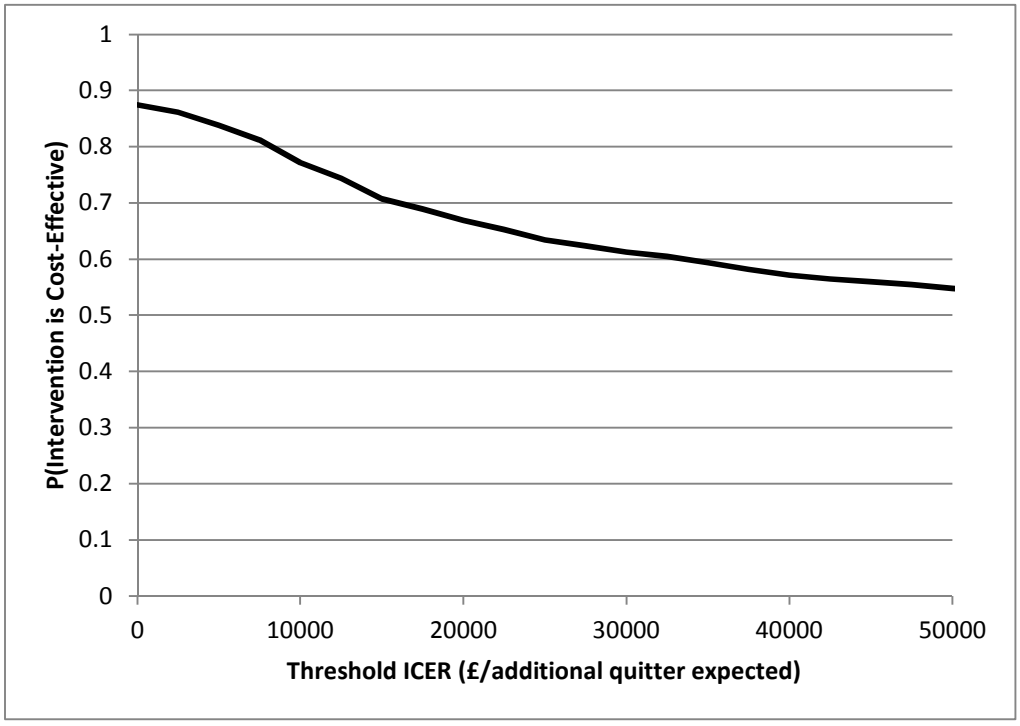


Table S2. Results of the incremental cost effectiveness analysis for women over 27

	Expected per-participant Costs (£ in 2012/13 prices)	Expected quit rate
Physical activity group	4968	0.101
Control group	4738	0.069
Difference	230	0.032
	Expected annual Costs ***(£ in 2012/13 prices)***	Expected annual quitters
Physical activity group	288,119	5.86
Control group	274,791	4.02
Difference	13,328	1.84
incremental cost effectiveness ratio (ICER	£7,200 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay above £7,200 per additional quitter. However, in context, a more reasonable interpretation is that there is no significant difference between the PA and control group results for either cost or effectiveness.	

Figure S3. Cost-effectiveness scatterplot (women over 27)

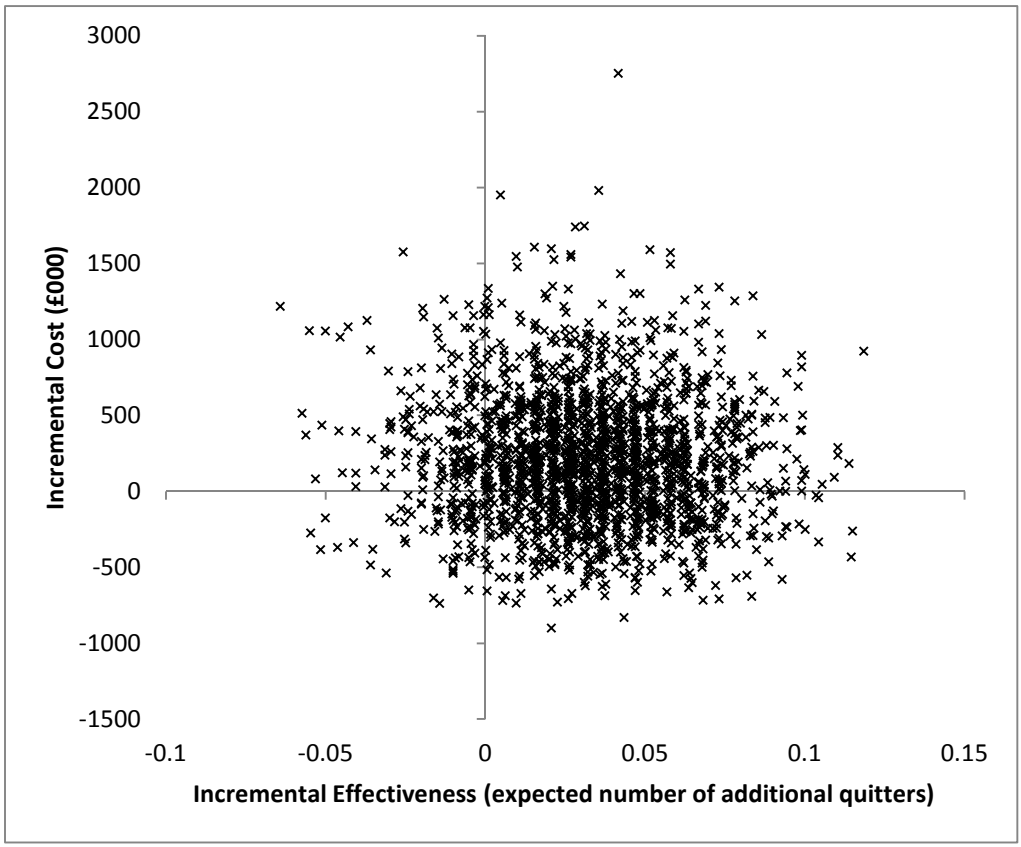


Figure S4. Cost-effectiveness acceptability curve (women over 27)

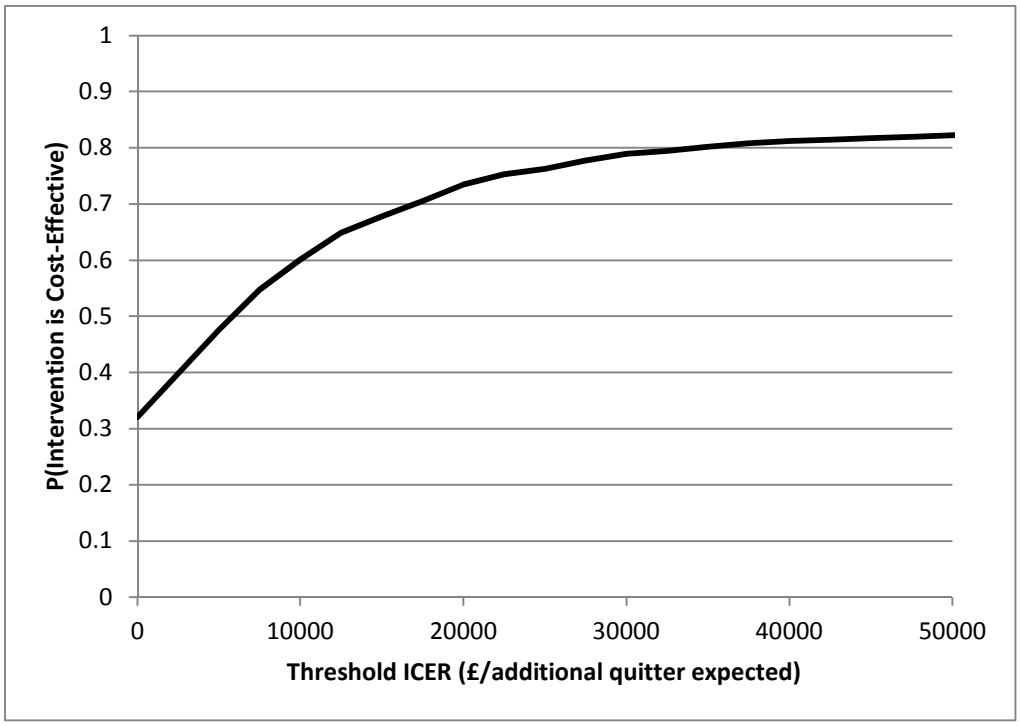


Table S3. Results of the incremental cost effectiveness analysis (FTCD<4)

	Expected per-participant Costs (£ in 2012/13 prices)	Expected quit rate
Physical activity group	4620	0.122
Control group	4435	0.084
Difference	185	0.037
	Expected annual Costs ***(£ in 2012/13 prices)***	Expected annual quitters
Physical activity group	267,945	7.06
Control group	257,242	4.89
Difference	10,703	2.17
incremental cost effectiveness ratio (ICER	£4,900 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay above £4,900 per additional quitter. However, in context, a more reasonable interpretation is that there is no significant difference between the PA and control group results for either cost or effectiveness.	

FTCD: Fagerstrom Test of Cigarette Dependence

Figure S5. Cost-effectiveness scatterplot (FTCD<4)

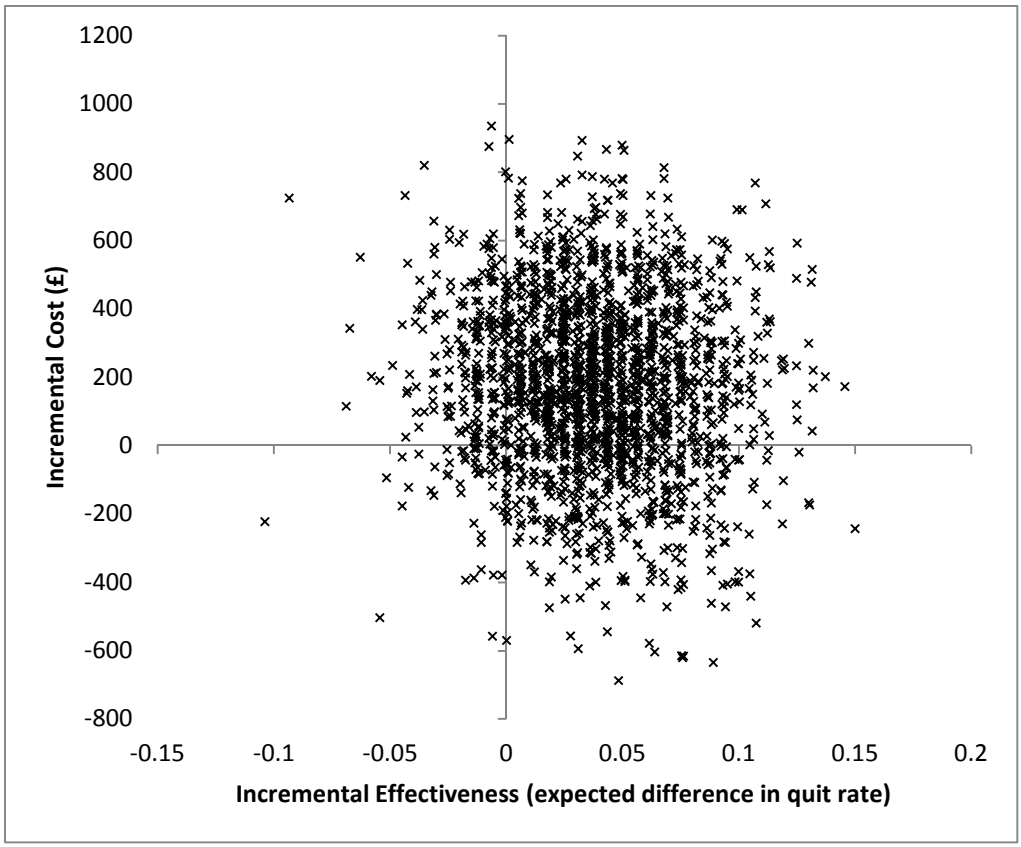


Figure S6. Cost-effectiveness acceptability curve (FTCD<4)

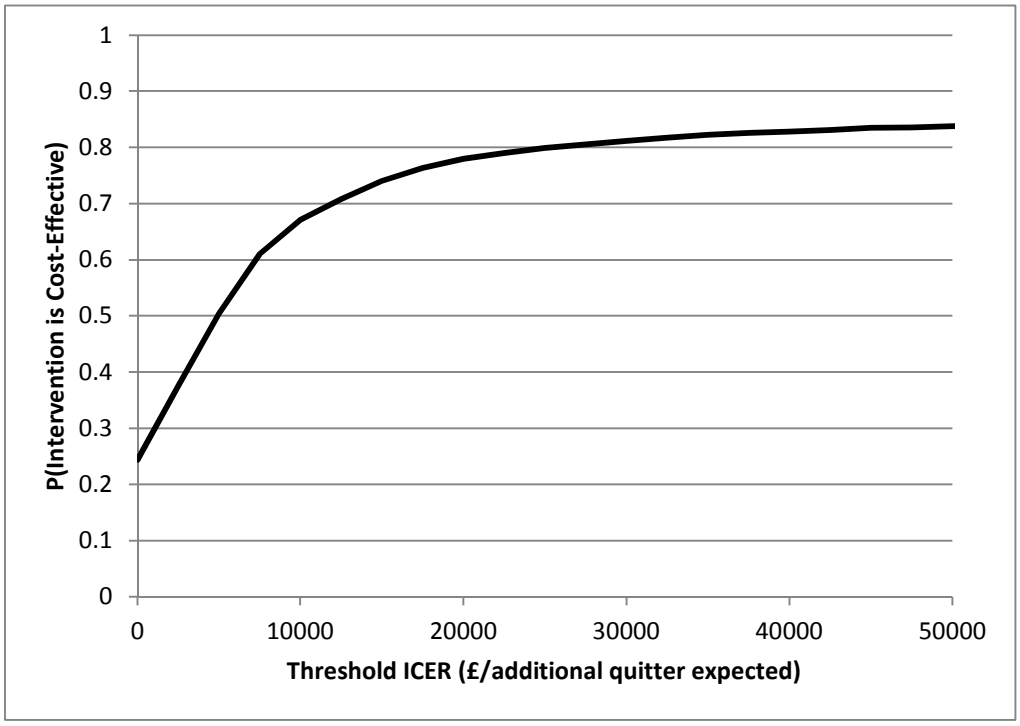


Table S4. Results of the incremental cost effectiveness analysis (FTCD≥4)

	Expected per-participant Costs (£ in 2012/13 prices)	Expected quit rate
Physical activity group	4772	0.0468
Control group	4976	0.0485
Difference	−204	−0.0016
	Expected annual Costs ***(£ in 2012/13 prices)***	Expected annual quitters
Physical activity group	276,788	2.71
Control group	288,630	2.81
Difference	−11,842	−0.10
incremental cost effectiveness ratio (ICER	£124,000 per quitter. Note that this result taken in isolation would suggest that PA should be preferred at any willingness to pay *below* £124,000 per additional quitter. This is because the differences in cost and effectiveness are both negative. However, in context, a more reasonable interpretation is that there is no significant difference between the PA and control group results for either cost or effectiveness.	

FTCD: Fagerstrom Test of Cigarette Dependence

Figure S7. Cost-effectiveness scatterplot (FTCD≥4)

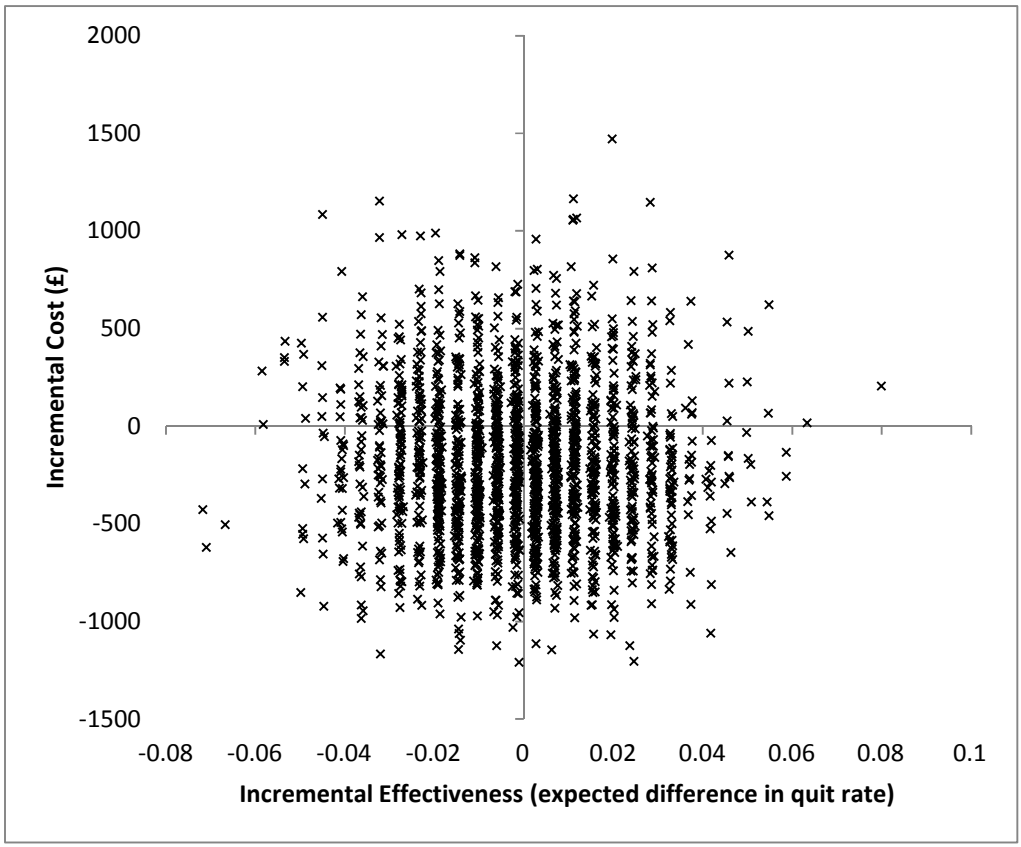
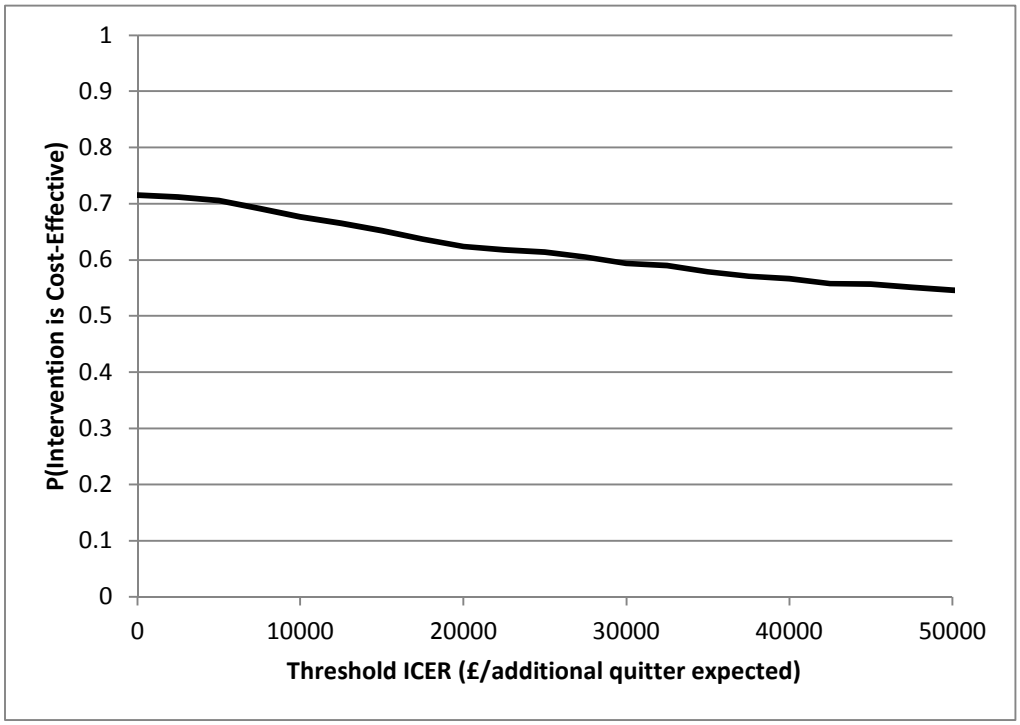


Figure S8. Cost-effectiveness acceptability curve (FTCD≥4)



APPENDIX 10: PATIENT AND PUBLIC INVOLVEMENT (PPI)

The LEAP trial was preceded by pilot work (Ussher M, Aveyard P, Coleman T, Strauss L, West R, Marcus B, Lewis B, Manyonda I (2008) Physical activity as an aid to smoking cessation during pregnancy: two feasibility studies. BioMed Central Public Health, 23, 328.) during which pregnant smokers and ex-smokers were interviewed concerning the recruitment methods, study design and interventions. The findings from these interviews were used in the design of the LEAP trial.

The Trial Steering Committee included a lay member who approved the protocol and checked the patient information sheet and consent form, as well as being involved in monitoring all stages of the study. This individual was also involved in discussions concerning the dissemination of the findings.

LEAP included qualitative interviews with women who were enrolled in the trial and with researchers delivering the interventions. This helped us to assess the acceptability of the intervention and their overall experience of being involved in the trial. These interviews also helped us to interpret the findings and to identify topics for future research.