A systematic review and economic evaluation of exercise referral schemes in primary care: A short report

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Contributions of authors

Fiona Campbell and Emma Everson-Hock designed the protocol for, and carried out the systematic review of clinical effectiveness. Sarah Davis, Mike Holmes and Nana Anokye designed and carried out the cost effectiveness analysis. Helen Buckley Woods carried out the searches. Eva Kaltenthaler and Paul Tappenden helped design the project and protocol and commented on draft versions of the report.

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1. LIST OF ABBREVIATIONS

Abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

LIST OF ABBREVIATIONS

7day PAR	7 day physical activity recall
BA	Brief Advice
BMI	Body mass index
BP	Blood pressure
CI	Confidence intervals
CHD	Coronary heart disease
ERS	Exercise referral scheme
EoP	Exercise on Prescription
GP	General practitioner
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
HADS	Hospital Anxiety and Depression Scale
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
RR	Risk ratio or relative risk
PA	Physical activity
PHAC	Public Health Appraisal Committee
PSA	Probabilistic sensitivity analysis
PSW	Physical self-worth
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QALY	Quality adjusted life-years
SD	Standard deviation
SF-12	Short form questionnaire -12 items
SF-36	Short form questionnaire – 36 items

2. EXECUTIVE SUMMARY

2.1 Background

2.1.1 Clinical effectiveness

There is a considerable body of evidence demonstrating the benefits of physical activity both in terms of treating and preventing diseases. Current recommendations suggest that adults should undertake at least 150 minutes of moderate intensity activity each week, yet according to the 2008 Health Survey for England, only 39% of men and 29% of women achieved these levels.

Interventions to promote increased levels of physical activity require a wide variety of approaches, with each facilitating small increments in behaviour change. These may include interventions targeted at the population level, such as changes in the environment as well as interventions targeted at the individual level, such as brief advice delivered in primary care. Physical activity can be promoted in primary care in different ways, including delivery of advice, provision of written materials, and referral to an exercise programme. The UK has seen an expansion in exercise referral schemes (ERS) over the past two decades but there are concerns that these might not produce sustained changes in physical activity beyond the typical programme length of 12 weeks. In 2006, the UK National Institute for Health and Clinical Excellence (NICE) advised that there was insufficient evidence to recommend the use of exercise referral schemes to promote physical activity other than as part of research studies where their effectiveness can be evaluated. Despite this recommendation, the schemes are still widely used.

The NICE guidance: 'Four commonly used methods to increase physical activity (2006), which included guidance for ERS drew on a review of evidence which included four randomised controlled trials (RCTs). An additional four studies have been included in the more recent Pavey *et al.,* review, three of which have been published since 2006.

The scope for this systematic review was to be an update of the Pavey *et al.,* systematic review of the evidence. However, this update is more limited than Pavey *et al.,* due to the time and resource constraints of this project. In this update we have not included observational studies to , explore issues of adherence and uptake, but we have used the data from the included RCTs and explored explanations given within the papers themselves. We have done this by qualitatively analysing the discussion and conclusion sections of the included trials and additionally identified qualitative studies undertaken as part of a mixed methods analysis of exercise referral.

2.1.2 Cost effectiveness

In 2011, Anokye *et al.*, published the results of a cost-effectiveness model of Exercise Referral Scheme (ERS) based on data from a systematic review of the effectiveness of ERS by Pavey *et al.,* They concluded that ERS is associated with a modest increase in lifetime costs and benefits and that the cost-effectiveness of ERS is highly sensitive to small changes in the effectiveness and cost of ERS and is subject to some significant uncertainty mainly due to limitations in the clinical effectiveness evidence base.

This model was later amended to inform the National Institute for Health and Care Excellence (NICE) Public Health appraisal of brief advice (BA) in primary care to promote physical activity (PH44).

The scope for the economic analysis of ERS for this brief report was to update the Anokye *et al.*, brief advice model with evidence from an updated systematic review on the effectiveness of ERS and to update the costs.

2.2 Objectives

To undertake a systematic review to re-assess the evidence for ERS in order to determine clinical effectiveness and estimate cost effectiveness using a previously developed Markov model.

2.3 Methods

2.3.1 Clinical effectiveness

The search strategies used in the Pavey *et al.*, (2011) systematic review of the evidence were used in this review. Searches were limited by English Language and a publication date of October 2009 to current. SPORTDiscus was not available to the research team, so Scopus via Elsevier was used and the "stage one" search was conducted in this data source. Key sports and exercise science journals have been covered as they are indexed in one or more of the databases listed below. The "Journal of Aging and Physical Activity" was found not to be indexed in the databases searched, hence this journal was hand-searched by scanning the electronic table of contents available at http://journals.humankinetics.com/japa-contents (2009-current and "in-press" articles).

Inclusion/Exclusion criteria:

- **Population**

  Any adult (aged 18 years or over) with or without a medical diagnosis and deemed appropriate for ERS.

- **Interventions**

  The ERS exercise/physical activity programme is required to be more intensive than simple advice and needs to include one or a combination of counselling (face-to-face or via telephone); written materials; supervised exercise training.

- **Comparators**

  Any control, for example usual ('brief') physical activity advice, no intervention, attention control or alternative forms of ERS.

- **Outcomes**

  Physical activity, physical fitness, health outcomes, adverse events, and uptake and adherence to ERS.

- **Study design**

  Any new RCT evidence, identified in searches of electronic databases published from October 2009 to the present. We also included any qualitative studies (sibling studies that were done alongside the RCT as part of a mixed methods study.

Titles and abstracts were examined for inclusion by two reviewers independently. Disagreement was resolved by consensus. Data were extracted and the data extraction tool was modelled on that used in the Pavey *et al.,* review. The Cochrane risk of bias tool was used to assess study quality.

Data from new studies published since 2009 was tabulated and discussed in a narrative review. The data from studies already identified and analysed by Pavey *et al.,* were used as published and data from new studies were integrated with it. Meta-analyses were used to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses. These meta-analyses used data published in the Pavey *et al.,* review, and new data were added.

In order to extend our understanding of the factors that predict uptake and adherence, we undertook a qualitative thematic analysis of the discussion and conclusion sections of the included RCTs. The terms 'adherence and uptake' can be used variably within the literature. Uptake refers to initial attendance, take up or enrolment. Adherence describes the level and duration of participation and the threshold for determining 'adherence' may vary in different

studies.Tobi et al 2012 The results were described in a narrative, and a logic model was used to explore and explain associations between multiple and varied barriers and facilitators to uptake and adherence of exercise referral schemes.

2.3.2 Cost effectiveness

The cost-effectiveness model used to inform PH44 was updated with evidence from the updated systematic review on the effectiveness of ERS and costs were uplifted to 2013. The model has a Markov structure and considers a cohort of 100,000 individuals aged 50 years who present in a physically inactive state and are given a referral to a service designed to increase physical activity that includes a physical activity or exercise programme compared to a control group with no referral to an exercise service. The age of the population was selected to reflect the populations enrolled in the studies providing evidence on the effectiveness of ERS. The model estimates the likelihood of becoming physically active and the consequent risk reduction this has on coronary heart disease (CHD), stroke and type 2 diabetes mellitus.

A lifetime horizon has been adopted to acknowledge the long-term benefits of physical activity. The economic perspective of the model is the NHS and personal and social services (PSS) in the UK. Costs and health benefits were discounted at an annual rate of 1.5% as recommended by the NICE guide to the methods of technology appraisal.

2.4 Results

2.4.1 Clinical effectiveness

Our search of electronic databases and searching relevant journals yielded 9627 titles, of which one primary study was judged to meet the inclusion criteria. This study was a mixed methods evaluation, incorporating RCT and qualitative evidence, undertaken in Wales in the UK. It was larger than previous studies, with 2160 participants. Earlier studies ranged in size from 52 to 943 participants. The total number of participants in all eight studies was 5190. Three studies were judged to be at moderate overall risk of bias and five to be at low overall risk of bias.

Referral to exercise referral schemes was in most instances made by the GP. In four of the studies, referral was made due to an individual's health risk that could be attenuated by increased levels of physical activity, most commonly risk of coronary heart disease. In the other four studies, patients were referred on the basis of being sedentary. Uptake, ie the initial attendance, take up or enrolment following referralranged from 35% to 100% in the included studies.

Adherence, ie, continued participation in the scheme ranged from 21.5% to 86%. Some suggested barriers included the lack of a specific appointment at invitation. Lack of private transport and deprivation were barriers to uptake and adherence. Older participants, and those referred for non-weight related coronary heart disease risk factors and those already moderately active at baseline were most likely to complete the programme.

The most consistently reported PA outcome across studies was the proportion of individual achieving 90-150 minutes of at least moderate-intensity activity per week. When pooled across studies the relative risk was RR 1.12 (95%CI 1.04 to 1.20) of achieving this outcome with ERS compared with usual care at 6-12 months follow-up. These results show a decrease in the relative risk found by Pavey *et al.,* (RR 1.16 (95%CI 1.03 to 1.30)). In the pooled ITT analyses, the proportion achieving the PA threshold in the ERS group compared with usual care was RR 1.08 (95%CI 1.00 to 1.17). This is also a reduction on the relative risk found by Pavey *et al.,* (1.11, 95% CI 0.99 to 1.25).

When total minutes of physical activity data were pooled, there was a significant increase in the number of minutes of physical activity per week in the ERS group; mean difference 55.10 (95% CI 18.47 to 91.73).

Examining subgroups, Murphy *et al.,* reported that referral and participation in ERS increased physical activity significantly for those referred for CHD risk factors (OR 1.29, 95%CI 1.04 to 1.60). However, among those referred for mental health reasons, either solely or in combination with CHD, there was no difference in physical activity between the ERS and normal care participants at 12 months follow up. The effect of being in the ERS group on all referrals was an increase in levels of physical activity at 12 months, but this finding was of borderline statistical significance (OR 1.19, 95%CI 0.99 to 1.43).

2.4.2 Cost effectiveness

Exercise referral gained 0.003 quality adjusted life years (QALYs) at an additional cost of £225 per person. The estimate for the mean incremental cost effectiveness ratio (ICER) in the probabilistic sensitivity analysis was £76,276.

All of the probabilistic sensitivity analysis (PSA) estimates show an incremental gain in both costs and QALYs, however there is reasonable uncertainty in the magnitude of that cost and

QALY gain. The probability that ERS is cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained is only 0.004.

In the univariate sensitivity analysis the results were very sensitive to increases in the effect of ERS on physical activity uptake, the protective effect of physical activity and the process utility gains (short-term improvements in health-related quality of life) associated with increased physical activity. Small changes in these parameters led to ICERs close to £30,000 per QALY gained. Conversely, sensitivity analyses which applied more conservative assumptions on efficacy, duration of protective effect and process utility gain resulted in ICERs over £100,000 per QALY.

2.5 Discussion

2.5.1 Clinical effectiveness

There is evidence that ERS schemes can lead to improvements in self reported levels of physical activity when compared to receiving advice only. Increasing age is a factor that appears to support uptake and adherence to ERS, as does a greater level of physical activity at baseline. There is some evidence that for patients referred with CHD risk factors, there is more likelihood of increases in levels of physical activity. It is not possible to identify what elements of the intervention support successful uptake of ERS, adherence to ERS and long term behaviour change. Qualitative evidence suggests that interventions which enable the development of social support networks might be beneficial in promoting adherence and long term improvements in levels of physical activity. Practical factors, such as accessibility of leisure centres also play a part in uptake and adherence. ERS seem to play a role in enabling previously active adults regain their levels of physical activity. They seem to be less effective in promoting uptake and adherence amongst deprived populations.

2.5.2 Cost-effectiveness

There are several limitations of the analysis based on the updated model. The model only estimates the impact of physical exercise on selected morbidities and there may be others that would benefit from physical activity. Were this included in the model the likely effect would be to lower the ICER but the magnitude is difficult to assess. The updated model also does not include the impact of adverse events or injuries, however available evidence suggests these are minor and would have little effect on the cost-effectiveness of ERS.

A limitation in assessing sub-groups (obesity, hypertension, depression) is that, with the exception of the depression subgroup, the efficacy of ERS is assumed to be the same as the whole inactive population. The model also assumes that the starting utility for these subgroups is the same as for the general population. Were the utility to be lower, this may lower the incremental QALY gains, resulting in a higher ICER.

We were unable to assess whether less intensive exercise referral schemes could be effective at a lower cost and therefore be cost-effective. The sensitivity analysis indicated that schemes would need a 60% reduction in costs to achieve an ICER below £30,000 per QALY gained. However, less intensive schemes may be less effective and so data on both effectiveness and costs would be required to assess cost-effectiveness.

The results are very sensitive to small changes in some of the model parameters. A relatively small increase in the efficacy of ERS or a three year increase in the length of the process utility gains both lead to ICERs that are below £30,000 per QALY gained. In contrast, removing the process utility attributed to ERS results in an ICER in excess of £180,000 per QALY gained and using efficacy data from the ITT analysis, which provides a more conservative estimate of effectiveness (RR, 1.08, 95%CI 1.00 to 1.17), resulted in an ICER of around £114,000.

The model over simplifies the clinical situation because it does not recognise that more than one of the three conditions can be present in the same individual and also that the presence of one comorbidity may impact the likelihood of experiencing another. We are constrained here to using an existing economic model in which type 2 diabetes, CHD and stroke are treated as mutually exclusive conditions. Also, the model does not account for the fact that stroke patients are at a higher risk of having recurrent strokes and thus the utility loss and additional costs associated with this are not taken into account. The impact of these limitations on the cost-effectiveness of ERS is difficult to estimate. It also excludes any long-term benefits of physical activity that fall outside of these three conditions.

2.6 Conclusions

Our analysis indicates that the ICER for ERS compared to usual care is around £76,000 per QALY, although the cost-effectiveness of ERS is subject to considerable uncertainty and is particularly sensitive to the assumptions made regarding the effectiveness ERS in increasing physical activity and the size and duration of process utility gains.

Post original report production:

Following production of the report, NICE requested further analyses on two occasions. These are included in Appendix 7 and 8.

3. BACKGROUND

3.1 Description of health problem

There is a considerable body of evidence demonstrating the benefits of physical activity both in terms of treating and also preventing diseases; including coronary heart disease, stroke, type 2 diabetes mellitus, chronic back pain, osteoporosis, cancers, depression and dementia.[1,2] Current recommendations from the Department of Health[1] suggest that adults should undertake at least 150 minutes of moderate intensity activity each week, (in the form of at least 30 minutes of activity on at least five days a week, which can be split into three 10 minutes bouts in the same day), yet according to the 2008 Health Survey for England, only 39% of men and 29% of women achieved these levels.[1]

Interventions to promote increased levels of physical activity require a wide variety of approaches, with each facilitating small increments in behaviour change.[3] These may include interventions targeted at the population level, such as changes in the environment as well as interventions targeted at the individual level, such as brief advice delivered in primary care. Over the last 10 years or so, there has been a shift in focus from promoting vigorous exercise to promoting moderate exercise, with more emphasis on lifestyle activity, due to the expanding body of evidence suggesting that there may be greater population gains through the least active becoming more active rather than moderately active people engaging in more vigorous forms of activity.[3]

3.2 Description of technology under assessment

Primary care has been recognised as a potentially valuable setting for the promotion of physical activity in those who might benefit most.[5] One commonly used method to increase physical activity is the use of exercise referral schemes (ERS). Exercise referral schemes have seen considerable growth, and are now the most common form of physical activity intervention in primary care.[4]

Exercise referral is the practice of referring a person from primary care to a qualified exercise professional who uses relevant medical information about the person to develop a tailored programme of physical activity usually lasting from 10-12 weeks. In so doing opportunities for exercise are provided and there is an expectation that levels of physical activity will increase, leading to positivechanges in health behaviours over the long term. These types of schemes

usually rely on a partnership between the local authority, Primary Care Trust and private leisure service providers.

4. DEFINITION OF THE DECISION PROBLEM

Since the early 1990s there has been a considerable growth in the number of exercise referral schemes in the UK.[5] By 2005, 89% of primary care organisation in England ran an ERS making it one of the most common forms of physical activity intervention in primary care.[4]

Five previous systematic reviews have been undertaken in this area (Morgan 2005,[6] Sorensen *et al.*, 2006,[7] NICE 2006,[8] Williams *et al.*, 2007,[9] Pavey 2011[10]) have been undertaken exploring the effectiveness of exercise referral schemes. There was a lack of consistency in the included studies in each of these reviews, revealing a different understanding and interpretation of ERS between authors. Despite these varying definitions, these previous systematic reviews conclude that ERS have a small effect in increasing physical activity in the short-term, with little or no evidence of long-term sustainability (i.e. 12-months or longer). There was also evidence of a reduced level of depression for participants given exercise referral compared to usual care.[10] However, owing to the considerable uncertainty surrounding the clinical effectiveness and cost-effectiveness of exercise referral schemes, in 2006, the NICE Public Health Intervention programme determined that there was insufficient evidence to recommend the use of ERS as an intervention, other than as part of research studies where their effectiveness could be evaluated.

The NICE guidance: 'Four commonly used methods to increase physical activity (2006[8]), which included guidance for ERS drew on a review of evidence which included four randomised controlled trials (RCTs - Taylor *et al.*, 1998,[11] Halbert *et al.*, 2000,[12] Lamb *et al.*, 2002,[13] Harrison *et al.*, 2005[14]). An additional four studies have been included in a more recent review (Pavey 2011[3]), three of which have been published since 2006 (Murphy *et al.*, 2012,[15] Duda *et al.*, 2014,[16] Issacs *et al.*, 2007[17]).

Physical activity can be promoted in primary care in different ways, including delivery of advice, provision of written materials, and referral to an exercise programme. The UK has seen an expansion in exercise referral schemes over the past two decades[5] but there are concerns that these might not produce sustained changes in physical activity beyond the typical programme length of 12 weeks.[20] In 2006, the UK National Institute for Health and Clinical Excellence (NICE)[18] advised that there was insufficient evidence to recommend the use of exercise referral schemes to promote physical activity other than as part of research studies where their effectiveness can be evaluated. Despite this recommendation, the schemes are still widely used.

A model-based economic evaluation of ERS concluded that the cost-effectiveness of ERS is highly sensitive to small changes in the effectiveness and cost of ERS and is subject to significant uncertainty mainly due to limitations in the clinical effectiveness evidence base (Anokye *et al.,* 2011[19]).

Given the considerable public health benefits of increasing levels of physical activity, it is important that any initiatives for its promotion are kept under consideration and review. Within this short report, newly available effectiveness evidence will be used to update the existing knowledge base and inform NICE guidance for ERS referred from primary care. The report will address the question: "what is the clinical effectiveness and cost-effectiveness of ERS to promote physical activity?" Key factors that will be addressed will include an analysis of effects for those referred for particular clinical conditions, and an exploration of sub-groups for whom intervention effectiveness might have a greater effect that in others, such as differences between genders, and age groups. We shall also explore where there may be differences in outcomes that relate to key elements of the intervention, such as frequency of contact with the exercise service. The economic evaluation will also build on previous work to explore whether the cost-effectiveness differs in those referred for particular clinical conditions (hypertension, obesity and depression).

Report methods for synthesis of evidence of clinical effectiveness

This report will be an update of the Pavey *et al.,*[3] systematic review of the evidence; updated searches will be carried out in order to identify new evidence. Any new evidence that is identified will be reviewed systematically and the findings integrated with those of the existing review. The scope of the review will be more limited than Pavey *et al.,*[3] due to the time and resource constraints of this project. We will only include RCTs and systematic reviews of RCTs to analyse effectiveness. We will use only the included RCTs to further explore issues of adherence and uptake. We will do this in two ways; we shall explore adherence and uptake in the trials, and examine explanations given within the papers by the authors. This will be done by qualitatively analysing the discussion and conclusion sections of the included trials as well as extracting data on the numbers of participants who were included in the trials and the drop out rates. In addition, using the included RCTs, we shall identify qualitative studies undertaken as part of a mixed methods analysis of exercise referral

Overall aims and objectives of assessment:

- To identify any new research evidence, that has become available since 2009 to inform the review of effectiveness of exercise referral schemes (ERS)
- To update the Pavey *et al.*,[3] review with any additional evidence
- To qualitatively analyze the 'Discussion and Conclusion' sections of the included studies to identify potential barriers and facilitators to the implementation, uptake and adherence to ERS
- To explore, where data allows, any characteristics of the intervention or the population that might influence the effectiveness of the intervention
- To update the cost-effectiveness evaluation with any new evidence that has become available

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

- Identification of studies

The search strategy comprised the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The search strategies used in the Pavey *et al.*, (2011) systematic review of the evidence were used in this review. This consisted of two search strategies ("stage one" and "stage two"), details of which are included in Appendix 2 of this report. The stage one search was a focussed phrase search with stage two being a more sensitive search combining the terms for exercise referral with study type and setting terms (primary care). Searches were limited by English Language and a publication date of October 2009 to current. SPORTDiscus was not available to the research team, so Scopus via Elsevier was used and the "stage one" search was conducted in this data source. Key sports and exercise science journals such as "Medicine and Science in Sports and Exercise" and "International Journal of Sports Psychology" have been covered as they are indexed in one or more of the databases listed below. The "Journal of Aging and Physical Activity" was found not to be indexed in the databases searched, hence this journal was hand-searched by scanning the electronic table of contents available at http://journals.humankinetics.com/japa-contents (2009-current and "in-press" articles).

Sibling studies

In order to identify any sibling studies (qualitative studies conducted as part of a mixed method evaluation of the intervention), two searches were undertaken. Firstly, the names of authors and project names of the included trials papers were searched for in Google Scholar. To augment this search, citation searches of the included trials were undertaken in the Science Citation Index and proceedings and Social Science Citation Index and proceedings (via Web of Science Thomson ISI).

The following electronic databases were searched: MEDLINE and Medline in Process (via Ovid); EMBASE (via Ovid); PsycINFO (via Ovid); Scopus (via Elsevier); The Cochrane Library

including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) NHS Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE); Science Citation Index and proceedings and Social Science Citation Index and proceedings (via Web of Science Thomson ISI), UKCRN portfolio database; Current Controlled Trials; Clinical Trials.gov.

An example of the stage one and two search strategies is shown in Appendix 2.

Inclusion/Exclusion criteria:

- **Population**

  Any adult (aged 18 years or over) with or without a medical diagnosis and deemed appropriate for ERS.

- **Interventions**

  The ERS exercise/physical activity programme is required to be more intensive than simple advice and needs to include one or a combination of counselling (face-to-face or via telephone); written materials; supervised exercise training. Programmes or systems of exercise referral initiated in secondary or tertiary care, such as conventional comprehensive cardiac or pulmonary rehabilitation programmes, will be excluded. We will exclude trials of exercise programmes for which individuals will be recruited from primary care, but there was no clear statement of referral by a member of the primary care team.

- **Comparators**

  Any control, for example usual ('brief') physical activity advice, no intervention, attention control or alternative forms of ERS.

- **Outcomes**

  Physical activity (self-report or objectively monitored), physical fitness (e.g. maximal oxygen uptake (VO_{2max}), health outcomes (e.g. blood pressure), adverse events (e.g. musculoskeletal injury), and uptake and adherence to ERS. We will also explore how patient characteristics, (age, gender and diagnosis) and programme factors (e.g. length and intensity of the exercise programme) that might influence the outcome of ERS.

- **Study design**

  We included any new RCT evidence, identified in searches of electronic databases published from October 2009 to the present. Data were extracted and the data extraction tool was modelled on that used in the Pavey (2011) review. We also searched for any

systematic reviews published from 2009 to present of exercise referral schemes. Their lists of included studies were hand searched to identify any further relevant studies.

For any new RCTs that we identified, any qualitative data that has been reported as part of a mixed methods evaluation an ERS intervention were also included.

Any on-going studies that we identify will also be reported. These would offer the most relevant insights into the particular factors influencing the adherence and uptake of that particular ERS intervention.

Titles and abstracts were examined for inclusion by two reviewers independently. Disagreement was resolved by consensus.

- **Exclusion criteria**
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Quality assessment strategy

The Cochrane risk of bias tool was used to assess study quality (Higgins & Altman 2008[20]). Consideration of study quality included the following factors:

Trial characteristics:

1. Method of randomisation
2. Allocation concealment
3. Blinding
4. Numbers of participants randomised, excluded and lost to follow up.
5. Whether intent to treat analysis has been performed
6. Methods for handling missing data
7. Baseline comparability between groups

- **Methods of analysis/synthesis**

Data from new studies published since 2009 were tabulated and discussed in a narrative review. The data from studies already identified and analysed by Pavey *et al.,*[3] were used as published and data from new studies were integrated with it.

Meta-analyses were used to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses. These meta-analyses used data published in the Pavey *et al.,*[3] review, and new data were added.

Meta-analysis was carried out using fixed and random effects models, using Review Manager software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

In order to extend our understanding of the factors that predict uptake and adherence, we undertook a qualitative thematic analysis of the discussion and conclusion sections of the included RCTs. This yielded insights into the factors identified by the trialists that influenced variations in uptake or adherence. The results will be described in a narrative, and a logic model used to explore and explain associations between multiple and varied barriers and facilitators to uptake and adherence of exercise referral schemes.

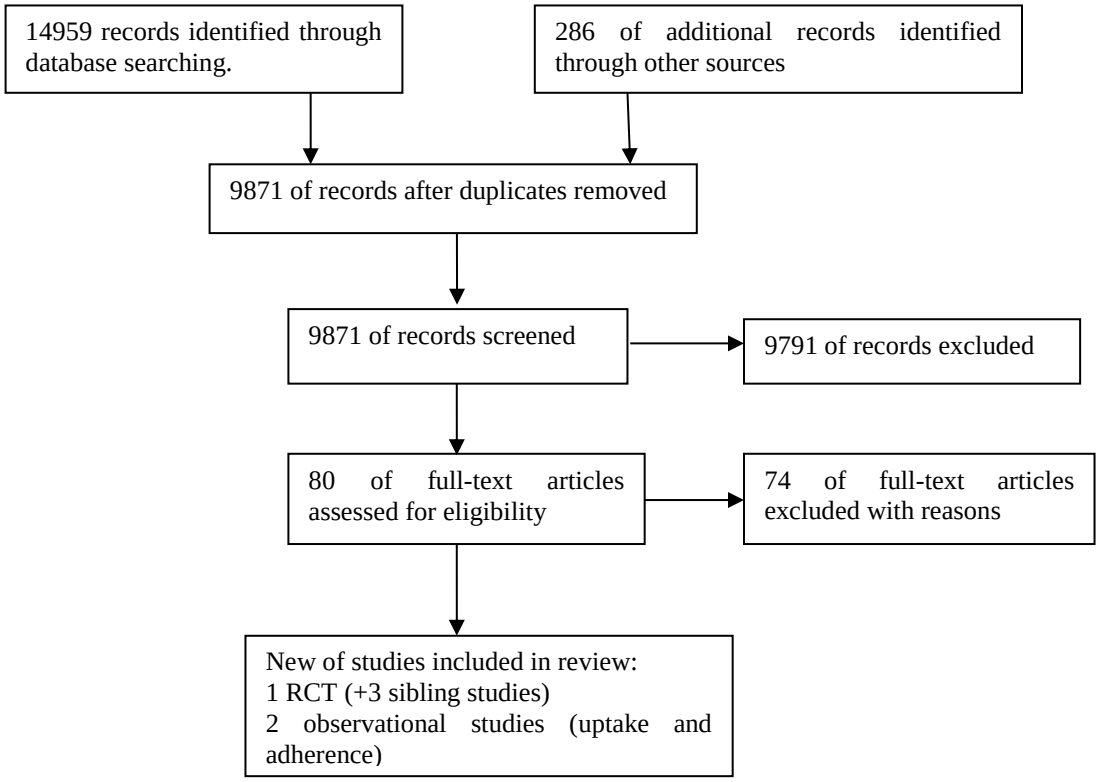
5.2 Results

5.2.1 Quantity and quality of research available

Our search of electronic databases and searching relevant journals yielded 9627 titles, of which one primary study was judged to meet the inclusion criteria. Figure 1 summarises the process of identifying the inclusion and exclusion process. In two studies[24,25] additional data were supplied by the authors. One study,[21] identified in bibliographic searching, could not be retrieved. The main reasons for excluding studies included: non-RCT design (n=44), participants recruited from primary care for inclusion in an exercise programme but without referral from a health care professional (n=20), the intervention was a prescription to undertake exercise but not a referral to a third party exercise provider (n=5), the population were not appropriate (n=1), participants were already part of an intervention prior to randomisation (n=1), or randomisation occurred prior to the baseline assessment (n=1). Appendix 5 provides the full list of excluded studies. The

included studies are summarised in Table 1, it includes the studies incorporated in the Pavey *et al.*, review. The new evidence is highlighted in bold type within the tables.

Figure 1: Flow diagram demonstrating the process of identifying new studies for inclusion in the review



5.2.2 Characteristics of included studies

The characteristics of the included ERS studies are summarised in Table 2. All of the included studies were RCTs. The Pavey *et al.,*[3] review included seven studies (10 publications). The data from these studies are included in the tables of this review, with new data emboldened. One additional study was identified (4 publications).[25,27-29] This study was a mixed methods evaluation, incorporating RCT and qualitative evidence, undertaken in Wales in the UK. It was larger than previous studies, with 2160 participants. Earlier studies ranged in size from 52 to 943 participants. The total number of participants in all eight studies was 5190.

The studies of Duda *et al.,*[22] and Gusi *et al.,*[30] used cluster allocation, with the other studies using individual level randomisation. Follow-up duration ranged from 2 to 12 months. The GP was the main referrer, usually using a bespoke referral form to a fitness or exercise instructor/officer. The Murphy *et al.,*[25] study, included referrals by health professional working in a range of health care settings.

Six studies[13,16,19,25,30,31] compared ERS with a 'usual care' group, which consisted of no exercise intervention or simple advice on physical activity. Sorensen *et al.,*[23] compared ERS with motivational counselling aimed at increasing daily physical activity (PA). The Isaacs *et al.,* study[17] also included an instructor-led walking programme. The Duda *et al.,* study[16] compared two forms of ERS, i.e. standard ERS versus a combined ERS plus self-determination theory (SDT) – based intervention.

All of the studies recruited participants who were sedentary or who were believed by their GP to be able to improve health by an increased physical activity level. They all also excluded individuals who had poorly controlled hypertension, diabetes or heart disease. Gusi *et al.,*[30] also excluded those with severe obesity or major depression. Sorensen *et al.,*[23] included participants who were willing to pay 750 Danish krone for the intervention.

The participants included in the Murphy *et al.,*[25] study shared a similar profile to those already included in earlier studies. Most of those recruited were middle-aged white adults with at least one medical condition that might benefit from an increased level of physical activity (see Table 4). In the Murphy *et al.,*[25] study, 72% or participants had coronary heart disease (CHD) risk factors and 24% had mental health problems.

Interventions ran for between 10 weeks[13,19,31] and 6 months[30], and included instructor-led exercise classes or walks[30], some form of consultation aimed at increasing activity[24,31] or a combination of the two.[13,16,19,25,32] The intervention by Sorensen *et al.*,[23] was based on the transtheoretical model of behaviour change, which categorises people into stages of readiness for change and postulates 10 experiential and behavioural processes of change, pro and con beliefs and self-efficacy beliefs (beliefs in personal ability to carry out the behaviour in question).[24] The Duda *et al.*,[16] intervention was based on self-determination theory, which emphasises the determinants and consequences of different reasons for behavioural engagement, which vary in their degree of self-determination.[25] The intervention aimed to promote autonomy support, which is assumed to foster participants' feelings of competence, autonomy and relatedness and, as a result, enhance autonomous motivation for physical activity and associated mental health outcomes.[16] The only study added since the Pavey HTA[3], by Murphy *et al.*,[25] was also the only study to explicitly use motivational interviewing (MI). However, fidelity to this intervention method during consultations was considered to be low. Motivational interviewing is, "a collaborative, person-centred form of guiding to elicit and strengthen motivation for change" (p.137).[26] In those that held supervised exercise sessions or walks, the number of sessions per week varied between one[25] and three[30], with the most common being two sessions per week[13,16,19] although one study[23] held one session per week for the first two months and then two sessions per week for the following two months. Supervised exercise sessions or walks lasted between 30-40 minutes[11] and an hour.[16,32] Two interventions were group interventions[30,32] and four were at group and/or individual level.[13,16,24,25]

Table 1: Summary of characteristics of included ERS trials

Study	No of GP practices	Date study conducted	RCT design	Overall n	Randomised (n) (ERS/control)	Follow-up periods
[a]Taylor *et al.*,[11] UK	3	January to December 1994	Individual	142	97/45	8, 16, 26 and 37 weeks
Stevens *et al.*,[27] UK	1	Not stated		714	363/351	8 months
Harrison *et al.*,[14] UK	46	March 2000 to December 2001		545	275/270	6, 9 and 12 months
Isaacs *et al.*,[17] UK	88	October 1998 to April 2002		943	317/315/311	10 weeks, 6 and 12 months
[a]Sorensen *et al.*,[23] Denmark	14	2005–6	Individual	52	28/24	4 and 10 months
Gusi *et al.*,[30] Spain	4	Not stated	Cluster	287	127/160	6 months
Duda *et al.*, [16] UK	Not reported (13 leisure centre sites)	November 2007 to July 2008	Cluster	347	184/163	3 and 6 months
Murphy *et al.*,[25] UK	**12 local health boards**	**Not stated. NERS scheme rolled out in 2007**	**Individual**	**2160**	**1080/1080**	**6 and 12 months**

max., maximum; ref., reference; SDT, self-determination theory.

[a] Taylor *et al.*, provided three publications[13,36,37] from which data were extracted; for ease of reading, ref.[11] shall be used, with ref.[28] used for the Psychological well-being section. Sorensen *et al.*, provided two publications[32,38] from which data were extracted; for ease of reading, ref.[23] shall be used.

Table 2: Summary of inclusion and exclusion criteria for included ERS trials

Study	Age range of patients (years)	Inclusion criteria	Exclusion criteria	Inclusion/exclusion criteria determined/evaluated by	No. of participants excluded
Taylor *et al.*,[11] UK	40–70	Smokers, hypertension (140/90 mmHg), overweight (BMI > 25)	SBP > 200 mmHg, history of MI or angina pectoris, diabetes mellitus, musculoskeletal condition preventing PA, previous ERS referral	Research team and GP determined and evaluated	44
Stevens *et al.*,[27] UK	18+	Sedentary–less than 20 × 30 minutes of moderate-intensity PA or less than 12 × 20 vigorous-intensity PA in the last 4 weeks	Medical reasons for exclusion, e.g. registered disabled, diagnosis of heart disease	Research team determined and evaluated	113
Harrison *et al.*,[14] UK	18+	Sedentary, participating in < 90 minutes of moderate/vigorous PA a week, additional CHD risk factors; obesity, previous MI, on practice CHD risk management register, diabetes	GP identified contradiction to PA, SBP > 200 mmHg, not sedentary, only one family member (to avoid contamination–research team criterion)	GP evaluation using the trial's ERS-determined Criteria	285
Isaacs *et al.*,[17] UK	40–74	Not active (no definition reported), raised cholesterol, controlled mild/moderate hypertension, obesity, smoking, diabetes, family history of MI at early age	Pre-existing overt CVD, uncontrolled hypertension, uncontrolled	GP evaluation using criteria determined by an existing ERS	Not reported

Study	Age range of patients (years)	Inclusion criteria	Exclusion criteria	Inclusion/exclusion criteria determined/evaluated by	No. of participants excluded
			insulin-dependent diabetes, psychiatric or physical conditions preventing PA, conditions requiring specialist programme		
Sorensen *et al.*,[23] Denmark	18+	Patients must me*et al.*,l criteria: (1) having medically controlled lifestyle diseases or at risk of developing lifestyle diseases; (2) motivated to change lifestyle; (3) believed by the GP to be able to improve health from an increased PA level; and (4) willing to pay 750 Danish krone (€100) for the intervention	Not meeting the inclusion criteria	GP evaluation using the trial's ERS-determined criteria	Not reported
Gusi *et al.*,[30] Spain	60+	Moderately depressed (6–9 points on the Geriatric Depression Scale), overweight (BMI 25–39.9), capable of walking for more than 25 minutes	Severe obesity, major depression, debilitating medical condition, known unstable cardiac condition, attention or comprehension problems	Research team determined, GP evaluation	32
Duda *et al.*, [16] UK	18+	People with two or more major risk factors of coronary heart disease: • family history of CHD, smoking, raised cholesterol • obese (BMI > 30 or BMI > 25 plus one other risk factor) People suffering from well-controlled chronic medical conditions: • mild or controlled asthma, chronic bronchitis, controlled diabetes mellitus, mild-to-moderate depression and/or anxiety, people for whom the onset of osteoporosis may be delayed through regular exercise: i.e.	Angina pectoris, moderate-to-high (or unstable) hypertension ≥ 160/102 mmHg Poorly-controlled insulin dependent	GP evaluation using the trial's ERS-determined criteria	Not reported

Study	Age range of patients (years)	Inclusion criteria	Exclusion criteria	Inclusion/exclusion criteria determined/evaluated by	No. of participants excluded
		post-menopausal women, borderline hypertensive patients with a blood pressure no higher than 160/102 mmHg prior to medication, people exhibiting motivation to change	diabetes, history of MI within the last 6 months – unless the patient has completed stage III cardiac rehabilitation, established cerebrovascular disease, severe chronic obstructive airways disease, uncontrolled asthma		
Murphy *et al.*,[29] UK	**>16 years**	**The patient must be sedentary (defined as not moderately active for >3times per week or deconditioned through age or inactivity) and have at least one of the following medical conditions : CHD risk factors (raised BP, BMI>28, controlled diabetes, impaired glucose tolerance, raised cholesterol, family history of heart disease or diabetes, referral from cardiac rehab schemes) Mental health (mild anxiety, depression or stress) Musculoskeletal (at risk of osteoporosis, arthritis, poor mobility, musculoskeletal pain) Respiratory/pulmonary (COPD, Mild/well controlled asthma, bronchitis, emphysema) Neurological conditions (multiple sclerosis) Other (smoking, chronic fatigue)**	**Aged ≤ 16 years, unstable angina, blood pressure uncontrolled or above 180/100, cardiomyopathy, uncontrolled tachycardia, cardiac arrhythmia, valvular heart disease, congenital heart disease, unexplained dizzy spells, excessive or**	**Clinicians in normal practice referred to evaluation team**	**1493**

Study	Age range of patients (years)	Inclusion criteria	Exclusion criteria	Inclusion/exclusion criteria determined/evaluated by	No. of participants excluded
			unexplained breathlessness on exertion, uncontrolled diabetes, uncontrolled epilepsy, history of falls or dizzy spells in previous 12 months, uncontrolled asthma, first 12 weeks of pregnancy, awaiting medical investigation, aneurysms, history of cerebro-vascular disease, unstable or newly diagnosed angina, established CHD, any other uncontrolled condition		

BMI, body mass index; MI, myocardial infarction.

Table 3: Summary of participant characteristics of included ERS trials

study	Age		Gender (% male)		Ethnicity (%)		Reported diagnosed conditions for risk factors (%)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Taylor *et al.*,[11] UK	54.1	54.4	37	38	Not reported	Not reported	Smokers: 43% Overweight: 77% Hypertensive: 46%	Smokers: 40% Overweight: 71% Hypertensive: 58%
Stevens *et al.*,[27] UK	59.1	59.2	40	44	White: 87 Black: 5 Asian: 4 Other: 4	White: 83 Black: 4 Asian: 6 Other: 5	BMI > 25: 46 Smoker: 18	BMI > 25: 42 Smoker: 17
Harrison *et al.*,[14] UK	18–44 = 111 45–59 = 101 > 60 = 63	18–44 = 107 45–59 = 98 > 60 = 65	33	34	White: 71.9	White: 74.1	Smoker: 24.4 At least one CHD risk factor: 75.3	Smoker: 20.7 At least one CHD risk factor: 75.2
Isaacs *et al.*,[17] UK	57.1	Usual care: 57 Walk: 56.9	ERS: 35	32 Walk: 31	White: 75.7 Asian:16.7	(Control/ walking) White: 76.5/75.9 Asian: 14/12.2	(Exercise/ walking) Raised cholesterol: 24.0 Hypertension: 44.5 Obesity: 65.9 Smoking: 10.4 Type 2 diabetes: 12.3/11.3 Family history of MI: 13.9	(Control/walking) Raised cholesterol: 17.1/21.5 Hypertension: 43.5/46.3 Obesity: 63.5/58.5 Smoking: 8.3/12.2 Diabetes: 15.6/11.3 Family history of MI: 16.2/12.9
Sorensen *et al.*,[23] Denmark	53.9	52.9	43	37	Not reported	Not reported	Metabolic syndrome: 36 Type 2 diabetes: 18 CVD: 32 Other diseases: 14	Metabolic syndrome: 25 Diabetes: 21 Heart disease: 42 Other diseases: 13
Gusi *et al.*,[30]	71	74	0	0	Not reported	Not reported	Overweight	Overweight: 86

study	Age		Gender (% male)		Ethnicity (%)		Reported diagnosed conditions for risk factors (%)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Spain							(BMI>25): 80 Type 2 diabetes: 39 Moderate depression: 34	Type 2 diabetes: 37 Moderate depression: 38
Duda *et al.*, [16] UK	< 30: 19 30–49: 76 50–64: 64 65+: 25	< 30: 11 30–49: 77 50–64: 50 65+: 25	24	30	White: 74.9 Black: 10.6 Asian: 9.5 Other: 5	White: 67.5 Black: 14.9 Asian: 14.9 Other: 2.6	Smoker: 22.1 Hypertension: 38 Overweight (BMI > 25): 25.3 Obese (BMI > 30): 52.3 Morbidly obese (BMI>40): 12.1 Probable anxiety: 34.2 Probable depression: 21.9	Smoker: 23.1 Hypertensive: 37.5 Overweight: 26.3 Obese: 51.9 Morbidly obese: 13.5 Probable anxiety: 31.9 Probable depression: 15.3
Murphy *et al.*,[25] UK	**52 (SD 14.7)**		**44%**		**96% white**		**72% CHD risk factors 24% mental health issues**	

BMI, body mass index; MI, myocardial infarction.

Table 4: Summary of referral characteristics of included ERS trials

Study	Referrer	Format of referral	Referred to where	Participant cost	Referred to who
Taylor *et al.*,[11] UK	GP	Signed prescription card	Leisure centre	Half-price admission	Fitness instructor
Stevens *et al.*,[27] UK	GP	Letter	Leisure centre	Not reported	Exercise development officer
Harrison *et al.*,[14] UK	GP	Faxed referral form	Leisure centre	'Subsidised '	Exercise officer
Isaacs *et al.*,[17] UK	GP or practice nurse	Specially prepared 'prescription pad' – referral form	Leisure centre	Free	Fitness instructor
Sorensen *et al.*,[23] Denmark	GP	Not reported	Clinic	Pay €100	Physiotherapist
Gusi *et al.*,[30] Spain	GP	Not reported	Supervised walks in a public park or forest tracks	Not reported	Qualified exercise leaders
Duda *et al.*, [16] UK	Member of the primary-care team	Not reported	Leisure centre	Not reported	Health and fitness adviser
Murphy *et al.*,[25] UK	**Clinician**	**form**	**Evaluation team**	**Access to one to one exercise instruction and/or group exercise classes. Discounted rate for exercise activities, £1 per session**	**Evaluation team**

Table 5: Summary of ERS intervention characteristics of included ERS trials

Study	Initial screen/assessment	Scheme duration	Provider	Exercise sessions per week	Exercise session intensity	Group or individual	Exit assessment
Taylor *et al.,*[11] UK	Yes	10 weeks	Leisure centre	2 × 30–40 minutes	Moderate intensity	Group and/or individual	Not reported
Stevens *et al.,*[27] UK	Yes	10 weeks	Leisure centre	Not reported	Not reported	Not reported	Yes
Harrison *et al.,*[14] UK	Yes	12 weeks	Leisure centre	2 × 1 hour	Individually based	Group and/or individual	Yes
Isaacs *et al.,*[17] UK	Yes	10 weeks	Leisure centre	2 × 45 minutes	Not reported	Group and/or individual	
Sorensen *et al.,*[23] Denmark	Yes (and motivational counselling)	4 months	Clinic	First 2 months 2 sessions × 1 hour Second 2 months 1 session × 1 hour	More than 50% of heart rate reserve for a minimum of 20 minutes	Group	
Gusi *et al.,*[30] Spain	Not reported	6 months	Walking scheme	3 × 50 minutes	Not reported	Group	
Duda *et al.,* [16] UK	Yes	12 weeks	Leisure centre	Individually based	Individually based	Group and/or individual	
Murphy *et al.,*[25] UK	**With exercise professional on entry: lifestyle questionnaire, health check (resting heart rate, blood pressure, BMI and waist circumference), introduction to leisure centre facilities, motivation interview and goal setting**	**16 weeks**	**Exercise professionals**	**Access to one to one exercise instruction and/or group exercise classes.**	**4 week telephone contract with exercise professional – review of goals, motivational interview, relapse prevention.** **16 week consultation with exercise professional – review of goals, motivation interview, health check, lifestyle questionnaire, service evaluation questionnaire and advice on continuing with exercise after the programme** **8 months telephone contact**	**individual**	**12 months review including repeat of health check carried out at entry and Chester fitness step test.**

Study	Initial screen/assessment	Scheme duration	Provider	Exercise sessions per week	Exercise session intensity	Group or individual	Exit assessment
					by exercise professional to ask about their exercise behaviour and relapse prevention		

5.2.3 Risk of bias

Table 7 summarises the risk of bias for each of the included studies. Most included a power calculation and allocated participants using an appropriately generated random number sequence. However, the reporting of concealment of trial group allocation was poor, although there was good evidence of participant characteristics of intervention and control groups at baseline. Although blinding of participants and intervention providers in these studies was not feasible, blinding of outcome assessment was possible. Outcome blinding is particularly important in preventing assessment bias in the case of outcomes that require observer judgement or involvement (e.g. blood pressure measurement or exercise testing). Two studies[24,25] reported outcome blinding. Recall Questionnaire was assessed via telephone to maintain blinding. The reporting and handling of missing data were detailed for most studies, and all studies, except one[11] reported the use of intention-to-treat (ITT) analysis. The level of missing data at follow-up ranged across studies from 16.5% to 50%. Most studies used imputation methods (last observation carried forward or complete case average values) to replace missing data values at follow-up. Overall, three studies[13,16,31] were judged to be at moderate overall risk of bias and five[19,24,25,32] to be at low overall risk of bias.

Table 6: Summary of risk of bias assessment

Risk of bias criterion	Taylor *et al.*,[11] UK	Stevens *et al.*,[27] UK	Harrison *et al.*,[14] UK	Isaacs *et al.*,[17] UK	Sorensen *et al.*,[23] Denmark	Gusi *et al.*,[30] Spain	Duda *et al.*,[16] UK	Murphy *et al.*,[25] UK
Power calculation reported?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Method of random sequence generation described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes+	Yes
Method of allocation concealment described	Yes+	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes
Method of outcome (assessment) blinding described?	Unclear	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes
Were groups similar at baseline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was ITT analysis used?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there any statistical handling of missing data?	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Were missing data (dropout and loss to follow-up) reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

+, Correspondence with author red in Pavey *et al.,*

5.2.3 Exercise referral scheme eligibility, uptake and adherence

There was a considerable range in the proportion of individuals randomised compared with those deemed eligible (Table 8). In both the Sorensen *et al.*,[23] and Duda *et al.*,[16] studies, of those deemed eligible for ERS, a substantial number refused participation in the trial. In the Sorensen *et*

al.,[23] study this low number maybe reflective of the 750 Danish krone payment by patients as part of a standard Danish Exercise on Prescription (EoP). In the Duda *et al.,*[16] study, this may be related to the workload and training needs of the health and fitness advisors at the time of recruitment.

The terms 'adherence and uptake' can be used variably within the literature. Uptake refers to initial attendance, take up or enrolment. Adherence describes the level and duration of participation and the threshold for determining 'adherence' may vary in different studies.Tobi et al 2012.

Rates of uptake varied in the included studies. Taylor *et al.,*[11] Issacs *et al.,*[17] and Sorensen *et al.,*[23] Murphy *et al.,*[25] reported uptake rates in excess of 85%, in the Stevens *et al.,*[27] study only 126 (35%) of the 233 randomised to ERS attended the first consultation. Stevens *et al.,*[27] discussed how the low uptake they experienced may have been reflective of the nature of the invitation letter sent to participants and the point of randomisation (pre-invitation letter). Furthermore, they hypothesise that a change in the format of the letter (e.g. including a specific appointment date for the first ERS appointment) would have improved participation. Uptake was not reported by Duda *et al.,*[16] or Gusi *et al.,*[30]

Adherence was assessed differently between the trials and levels of adherence also varied. Stevens *et al.,*[27] and Gusi *et al.,*[30] reported ERS programme completion rates of 25% and 86%, respectively. However, these rates do not reflect the number of sessions attended, only those who attended a second consultation[27] or follow-up assessment.[30]

Sorensen *et al.,*[23] reported that an average 18 of a total of 24 ERS exercise sessions were attended and 68% and 75% of participants attended the counselling sessions at 4 and 10 months, respectively. Both Taylor *et al.,*[11] and Isaacs *et al.,*[17] provide a detailed description of ERS programme adherence. Taylor *et al.,*[11] reported 13% attending no exercise sessions and 28% attending 75–100% of exercise sessions, with an average of 9.1 out of 20 prescribed exercise sessions attended. Isaacs *et al.,*[17] reported 7.6% attending no exercise sessions and 42% attending 75–100% of exercise sessions in the leisure centre group. In the walking group, 23.5% attended no exercise sessions, with 21.5% attending 75–100% of exercise sessions. As shown in Table 8, there was no consistent difference in attendance rates between those in at-risk groups and

the overall study population in the studies of Taylor *et al.*,[11] and Isaacs *et al.*,[17] In the Isaacs *et al.*,[17] study, the 60- to 69-year age group had the highest adherence in both the ERS (53.3%) and the walking (24.2%) groups. There were no significant differences in attendance rate with employment status, educational level, socioeconomic status, ethnicity or relationship status. However, Murphy *et al.*,[25] did find differences in uptake and adherence between participants from deprived and less deprived areas. Adherence was lower for those without access to private transport in both the ERS and walking groups. Harrison *et al.*,[14] and Duda *et al.*,[16] did not provide information on participants' adherence to the ERS intervention.

Murphy *et al.*,[25] found that participants already active at baseline were the most likely to enter the exercise referral scheme, but also most likely to only partially attend a programme. Male and younger participants were slightly less likely to enter the scheme, and women less likely to complete the programme. Participants in the least deprived areas were more likely to take up the scheme, though the differences in adherence between the most and least deprived areas were smaller. Non-car owners were less likely to take up the scheme or to adhere to it if they joined. Those referred for mental health reasons were more likely not to enter the exercise referral scheme, while only one in three mental health patients completed the programme.

In a univariate regression analysis of predictors of uptake and adherence, the only significant correlates of uptake in the Murphy *et al.*,[25] study were car ownership and deprivation. Those in moderately deprived areas were less likely to enter than those in the least deprived areas. Car owners were significantly more likely to enter than non-car owners. Older participants, those referred for non-weight related CHD risk factors, non-mental health patients and those already moderately active at baseline were most likely to complete the programme.

In a multivariable regression analysis, the significant difference between low and medium deprivation areas remains and car ownership remains predictive of uptake. Associations of CHD risk factors with adherence become non-significant and associations of age and mental health status remain significant. Associations of baseline activity with adherence are strengthened in the multivariable analysis, with the contrast between 'inactive' and 'moderately inactive' participants becoming more significant. (see section 5.3 for further discussion of factors influencing uptake and adherence).

Table 7: Summary of eligibility and uptake figures for included studies

Study	No. deemed	Total n randomised	ERS (n)	Control (n)	ERS uptake

	eligible (n)				
Taylor *et al.*,[11] UK	345	142 (41%)+	97	45	85 (88%)
Stevens *et al.*,[27] UK	827	714 (86%)+	363	351	126 (35%)
Harrison *et al.*,[14] UK	830	545 (66%)+	275	270	232 (84%)
Isaacs *et al.*,[17] UK	1305	949 (73%)+	317	315 + 311	293 (92%)
Sorensen *et al.*,[23] Denmark	327	52 (16%)+	28	24	28 (100%)
Gusi *et al.*,[30] Spain	160	127 (79%)+	64	63	Not reported
Duda *et al.*, [16] UK	1683	347 (21%)+	184	163	Not reported
Murphy *et al.*,[25] UK	**3286**	**2160 (66%)**	**1080**	**1080**	**n=919 (85%)**

+, Percentage of individuals deemed eligible who were randomised.

Table 8: Proportion of individuals by risk group with 75-100% ERS attendance rates

Study	Smoking (%)	Obesity (%)	Hypertension (%)	Overall (%)
Taylor *et al.*,[11] UK	12	28	23	28
Isaacs *et al.*,[17] ERS group UK	45.5	38.8	46.1	42
Isaacs *et al.*,[17] control walking group UK	26.3	18.7	22.9	21.5

5.2.4 Assessment of effectiveness

Only Issacs *et al.*,[17] reported all outcome domains applicable to this systematic review (see Table 10). Where new data is added to the Pavey *et al.*,[3] review, it is emboldened within the tables.

Table 9: Summary of outcome domains assessed

Study	PA	PA measure	Physical fitness	Clinical outcomes	Psychological well-being	HRQoL	Patient satisfaction	Adverse events
Taylor *et al.*,[11] UK	Yes	Self report 7 day-PAR	Yes Sub-max HR	Yes BP, BMI, BF%, waist to hip	Yes PSW	No	No	No
Stevens *et al.*,[27] UK	Yes	Self report 7 day-PAR	No	No	No	No	No	No
Harrison *et al.*,[14] UK	Yes	Self report 7 day-PAR	No	No	No	No	Yes	No
Isaacs *et al.*,[17] UK	Yes	Self-report Minnesota LTPAQ	Yes Sub-max bike test Sub-max walking test	Yes BP, cholesterol, lipoproteins, triglycerides, weight, BMI, BF%, waist-to-hip ratio, FEV, PEF	Yes Anxiety, depression	Yes SF-36 mental	Yes	Yes GP records
Sorensen *et al.*,[23] Denmark	Yes	Self-report Unspecified	Yes Sub-max bike test	Yes Weight, BMI	No	Yes SF-12 mental, physical	No	No
Gusi *et al.*,[30] Spain	Not reported	N/A	No	Yes BMI	Yes Anxiety, depression	Yes EQ-5D	No	No
Duda *et al.*,[16] UK	Yes	Self report 7 day-PAR	No	Yes BMI	Yes Anxiety, depression	Yes Dartmouth QoL	No	No
Murphy *et al.*,[25] UK	**Yes**	**Self report 7 day-PAR**	**No**	**Measured at baseline**	**Yes HADs**	**Yes EQ-5D**	**Yes Client Service Receipt Inventory**	**No**

BF%, body fat %; BMI, body mass index; BP, blood pressure; EQ-5D, European Quality of Life-5 Dimensions; FEV, forced expiratory volume; HR, heart rate; LTPAQ, Leisure Time Physical Activity Questionnaire; N/A, not applicable; PAR, Physical Activity Recall; PEF, peak expiratory flow; PSW, physical self-worth; QoL, quality of life; SF-12, Short Form questionnaire-12 items; sub-max, sub-maximal.

5.2.4.1 Physical activity

All studies, with the exception of Gusi *et al.,*[30] provided a measure of self-reported PA. Self-reported measures included the validated 7-Day Physical Activity Recall Questionnaire (7-Day PAR)[13,25,31,32] and the validated Minnesota Leisure Time Activity Questionnaire.[17] None of the studies reported methods of measuring physical activity using an objective method of measurement, and all relied on self report tools.

ERS vs. Usual Care/Advice only

The most consistently reported PA outcome across studies was the proportion of individual achieving 90-150 minutes of at least moderate-intensity activity per week. Data for this outcome in the Murphy *et al.,*[25] study were supplied by the author (personal correspondence from Professor Murphy, October 8th 2013). When pooled across studies the relative risk was RR 1.12 (95%CI 1.04 to 1.20) of achieving this outcome with ERS compared with usual care at 6-12 months follow-up (see Figure 2). There was no evidence of heterogeneity in this analysis (I^2 0%). This analysis draws on data published by Pavey *et al.,*[3] Three studies[13,16,25] reported this outcome based on the number of individuals who were available at follow-up. These results show a decrease in the relative risk found by Pavey *et al.,*[3] (RR 1.16, 95%CI 1.03 to 1.30) In order to assess the potential (attrition) bias in using completers, the denominators of these three studies were adjusted to all individual randomised in order to perform an IT analysis (see Figure 3). It was assumed that all missing cases did not meet the PA threshold. In the pooled ITT analyses, the proportion achieving the PA threshold in the ERS group compared with usual care was RR 1.08 (95%CI 1.00 to 1.17). There was no evidence of heterogeneity in this analysis (I^2 0%). This is also a reduction on the relative risk found by Pavey *et al.,*[3] (RR 1.11, 95% CI 0.99 to 1.25).

Total minutes of physical activity was reported by Issacs *et al.,*[17] and Murphy *et al.,*[25] When this data were pooled, there was there was a significant increase in the number of minutes of physical activity per week in the ERS group; mean difference 55.10 (95% CI 18.47 to 91.73) (see Figures 4, 5 and 6).

Exercise referral scheme versus alternative physical activity intervention

Sorensen *et al.*,[23] reported a higher level of energy expenditure with ERS than with PA counselling. In contrast, the study by Isaacs *et al.*,[17] observed a higher level of PA (minutes of total and moderate-intensity activity, and energy expenditure) in those in the walking programme than in the ERS group. When pooled across studies, there was no significant difference in the total amount of physical or energy expenditure between ERS and alternative PA interventions (Figures 7 and 8).

Exercise referral scheme versus a Self Determination Theory informed delivery of Exercise on Referral

In the Duda *et al.*,[16] study, the proportion of patients achieving at least 150 minutes of moderate PA per week increased in the standard ERS group from 27% at baseline to 63% at 3 months and 46% at 6 months. There were no significant differences in these proportions between the standard ERS and a self determination theory informed delivery of ERS. (Table 10).

Subgroup analysis exploring the impact of patient variables on effects of ERS on levels of physical activity

Pavey *et al.*,[3] reported the following analysis of subgroups within seven studies: Harrison *et al.*,[14] reported no statistical significant interaction effects between the ERS effect and pre-specified baseline variables (i.e. CHD risk factors, sex and age). Comparing high adherers (>75% attendance at ERS) with low adherers (< 75% attendance at ERS in the Issacs *et al.*,[17] study, 32 high adherers and 16 low adherers were achieving >150 minutes of moderate PA per week at 10 weeks. At 6 months, 41 high adherers and 29 low adherers were achieving > 150 minutes of moderate PA per week. However, these proportions were not significantly different. In the Duda *et al.*,[16] study, age, gender, deprivation (Index of Multiple Deprivation score), ethnicity, depression at baseline and level of PA at baseline were assessed by regression methods as predictors of PA at 6 months. Only PA at baseline was associated with PA at the 6 month follow-up ($p<0.001$). Murphy *et al.*,[25] also found that effectiveness was highly dependent on adherence, with significantly greater differences in all outcomes among those who completed the 16 week programme compared with those who attended only partially or not at all.

Murphy *et al.*,[25] reported that referral and participation in ERS increased physical activity significantly for those referred for CHD risk factors (OR 1.29, 95%CI 1.04 to 1.60). However, among those referred for mental health reasons, either solely or in combination with CHD, there was no difference in physical activity between the ERS and normal care participants at 12 months follow up. The effect of being in the ERS group on all referrals was an increase in levels of physical activity at 12 months, but this finding was of borderline statistical significance (OR 1.19, 95%CI 0.99 to 1.43).

Table 10: Summary of PA data at follow-up

Study and time of follow-up	Patients achieving PA guidance (90-150 minutes/at least moderate-intensity per week)		Minutes per week at least moderate intensity				Total PA (minutes per week)		Energy expenditure (kcal/kg/day)	
	ERS, n/N	Control, n/N	ERS, mean (SD)		Control, mean (SD)		ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)
			Moderate	Vigorous	Moderate	Vigorous				
ERS vs. usual care										
Taylor *et al.*,[11]										
8 weeks[b]	51/63	20/31[c,d]	247 (174)	49 (60)	145 (178)[e]	21 (61)[e]	Not reported	Not reported	34.6 (1.2)	33.7 (1.7)[e]
16 weeks[b]	51/57	18/31[d,e]	226 (252)	59 (72)	160 (262)[c]	21 (72)[e]	Not reported	Not reported	34.6 (1.2)	33.9 (1.7)[e]
26 weeks[b]	39/47	18/31[d,e]	183 (234)	56 (108)	206 (251)[c]	34 (111)[c]	Not reported	Not reported	34.4 (1.8)	34.3 (1.2)[c]
37 weeks[b]	39/57	19/31[c,d]	158 (228)	42 (96)	162 (245)[c]	23 (106)[c]	Not reported	Not reported	34.1 (2.4)	33.9 (2.2)[c]
Stevens *et al.*,[27]										
8 months[f]	204/363	174/351[c,d]	Not reported		Not reported		Not reported	Not reported	Not reported	Not reported
Harrison *et al.*,[14]										
6 months[b]	38/168	22/162[d,e]	Not reported		Not reported		Not reported	Not reported	Not reported	Not reported
9 months[b]	36/149	31/140[c]	Not reported		Not reported		Not reported	Not reported	Not reported	Not reported
12 months[b]	40/155	32/157[c]	Not reported		Not reported		Not reported	Not reported	Not reported	Not reported
Isaacs *et al.*,[17]										
10 weeks[g]	48/164	29/157[d,e]	93 (115)		79 (114)[c]		584 (479)	668 (555)[c]	34 (26)	36 (32)[c]
6 months[g]	70/179	66/200[c,d]	65 (106)		58 (98)[c]		692 (496)	647 (463)[c]	38 (27)	35 (27)[c]
Gusi *et al.*,[30]	Not reported	Not reported	Not reported		Not reported		Not reported	Not reported	Not reported	Not reported
Murphy *et al.*,[25]										
12 months	**431/724**	**409/755**					**335.53 (442.47)**	**277.42 (371.70)**		
ERS vs. alternative PA intervention										
[h]Sorensen *et*										

Study and time of follow-up	Patients achieving PA guidance (90-150 minutes/at least moderate-intensity per week)		Minutes per week at least moderate intensity				Total PA (minutes per week)		Energy expenditure (kcal/kg/day)	
	ERS, n/N	Control, n/N	ERS, mean (SD)		Control, mean (SD)		ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)
			Moderate	Vigorous	Moderate	Vigorous				
al.,[23]										
4 months[b]	Not reported	Not reported	Not reported		Not reported		63 (114)	23 (107)[c]	43 (2.4)	41 (4.8)
10 months[b]	Not reported	Not reported	Not reported		Not reported		20 (124)	20 (152)[c]	41 (2.1)	40 (5)
Isaacs *et al.*,[17]										
10 weeks[g]	48/164	53/92[d,e]	93 (115)		113 (291)[c]		584 (479)	863 (1026)[e]	34 (26)	43 (38)[e]
6 months[g]	70/179	62/141[c,d]	65 (106)		89 (150)[e]		692 (496)	759 (539)[c]	38 (27)	42 (27)[c]
ERS vs. Self Determination Theory informed ERS										
Duda *et al.*,[16]										
3 months[g]	Not reported	Not reported	319 (338)[c]		331 (336)[c]		Not reported	Not reported	Not reported	Not reported
6 months[g]	66/156	83/169[c,d]	249 (356)[c]		246 (343)[c]		Not reported	Not reported	Not reported	Not reported

SD, standard deviation.

[a] Sorensen *et al.*,69 metabolic equivalent (METS)/hour/day.

[b] Numbers of individuals with complete data/questionnaires.

[c] Between-group difference not statistically significant at $p \leq 0.05$.

[d] The p-value calculated by authors of the present report.

[e] Between-group difference statistically significant at $p \leq 0.05$.

[f] All randomised participants.

[g] Provides b (patients achieving PA guidance) and f (all other PA measures).

[h] Mean change score

Figure 2: Number achieving 90-150 minutes PA/week (updated meta-analysis)

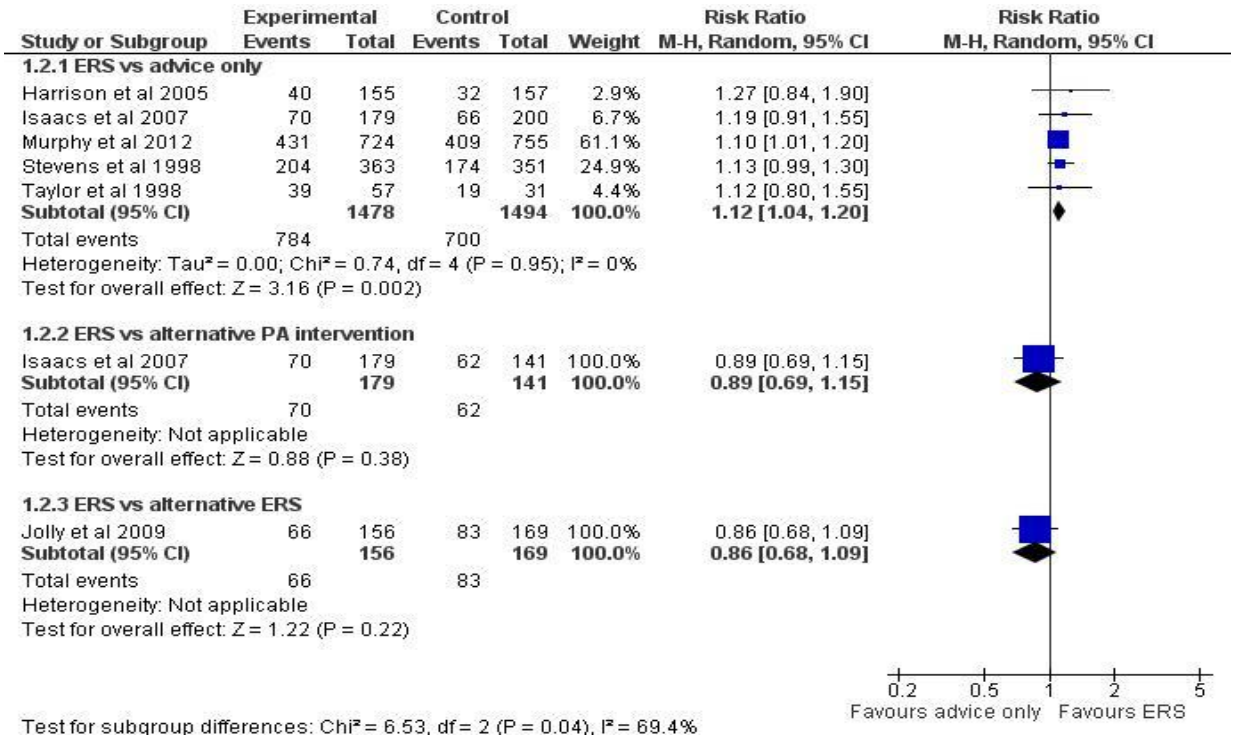


Figure 3: Number achieving 90-150 minutes PA/week (ITT analysis) (updated meta-analysis)

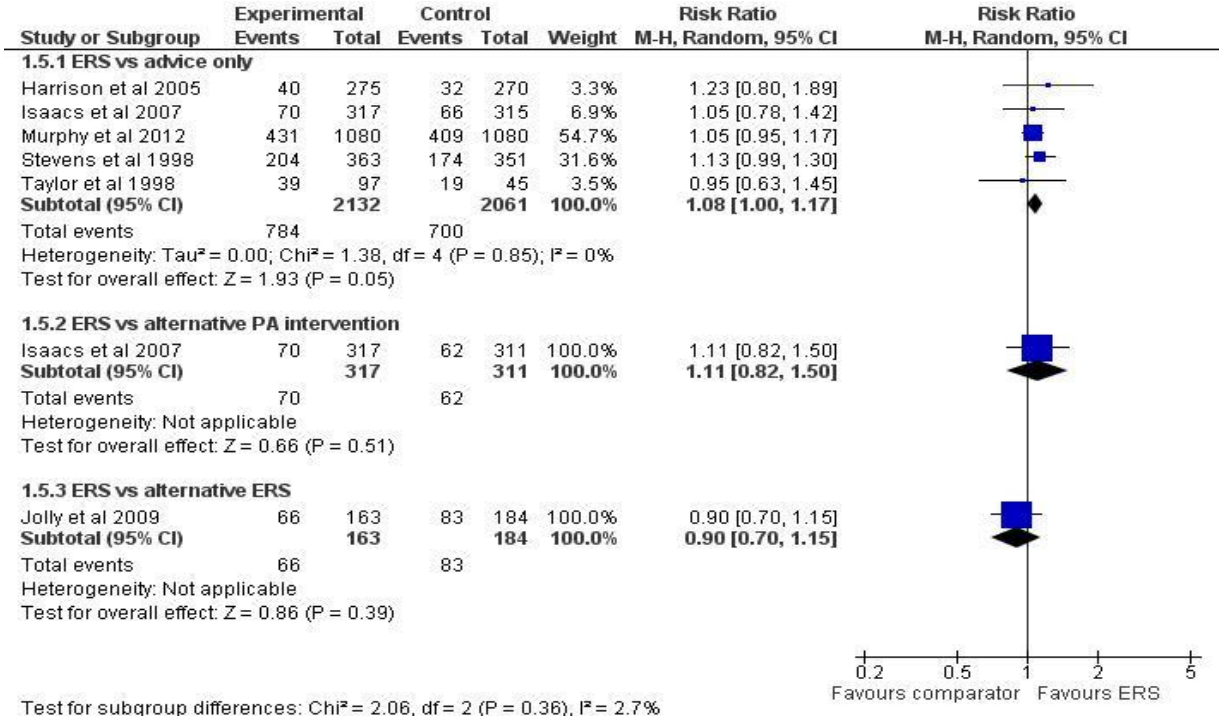


Figure 4: Minutes spent in at least moderate-intensity PA per week at 6-12 months follow-up[3]

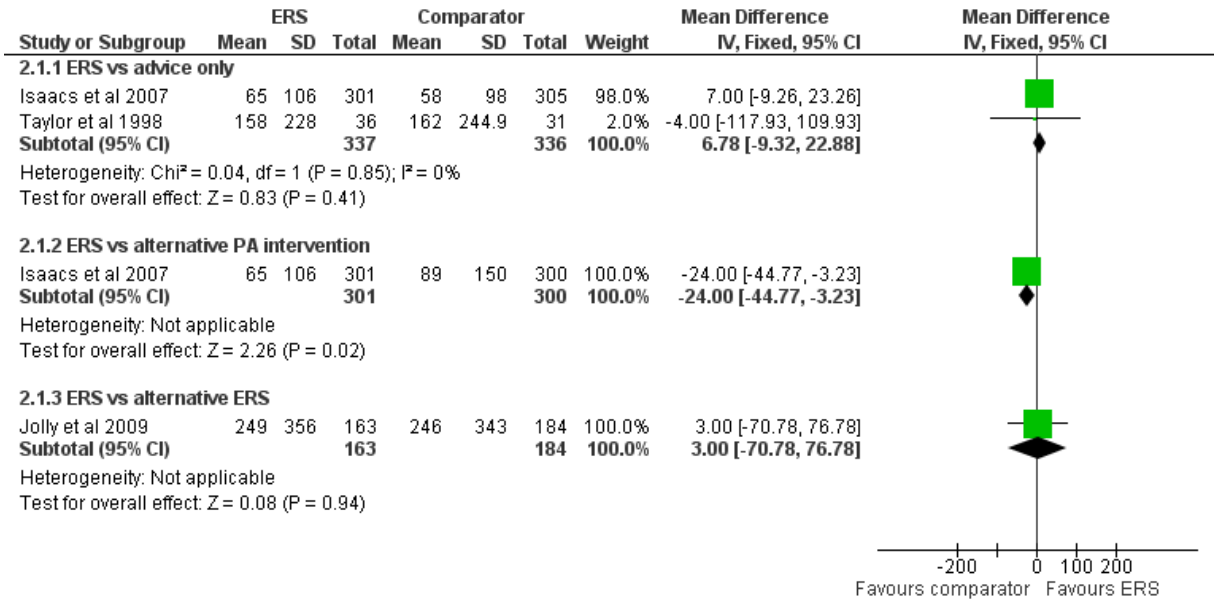


Figure 5: Minutes of total PA/week at 6-12 months follow-up ERS vs. advice only (updated meta-analysis)

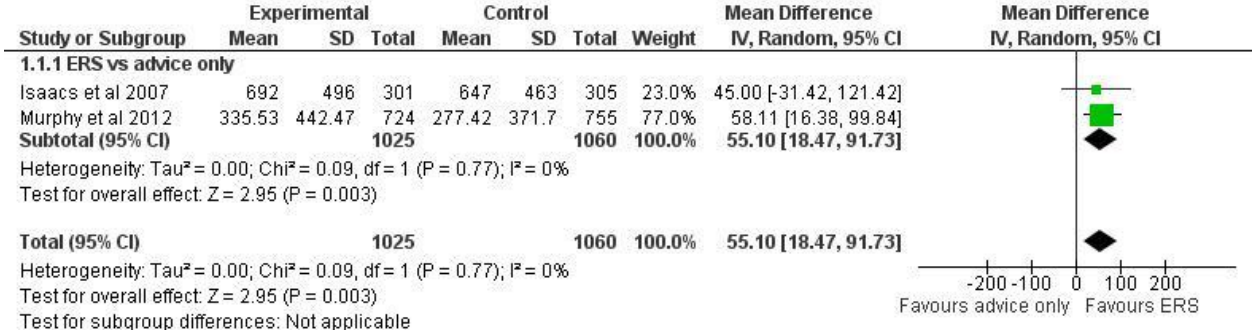


Figure 6: Minutes of total PA/week at 6-12 months follow-up ERS vs. alternative PA[3]

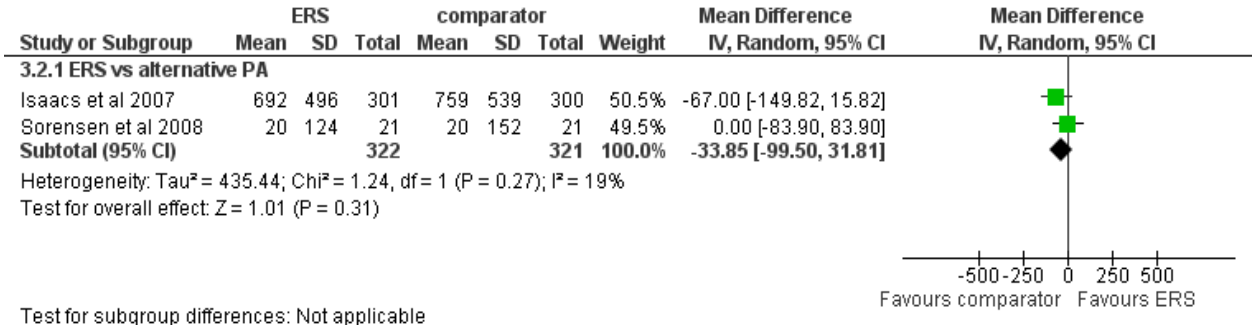


Figure 7: Energy expenditure (kcal/kg/day) ERS vs. usual care at 6-12 months follow-up[3]

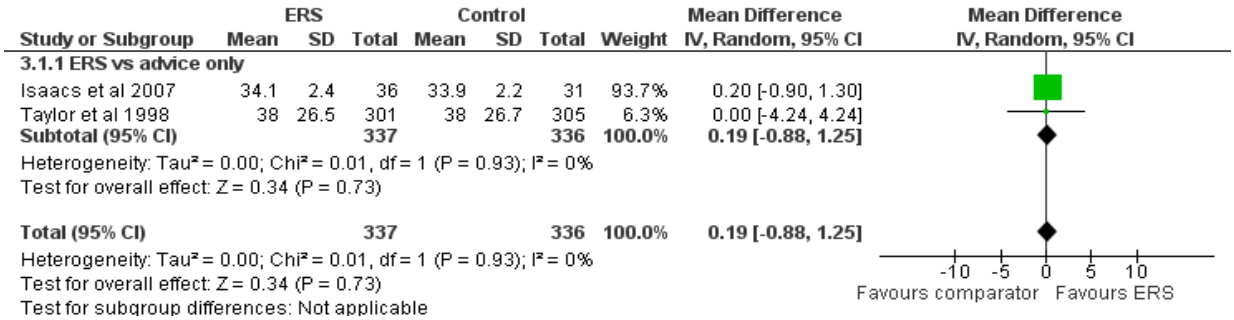


Figure 8: Energy expenditure ERS vs. alternative PA intervention at 5-12 months follow-up[3]

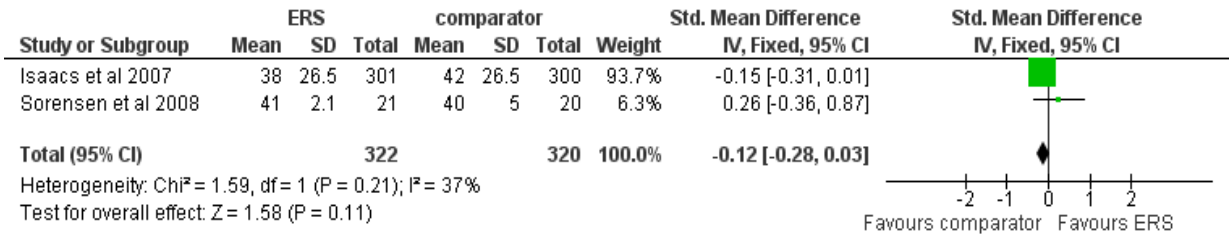
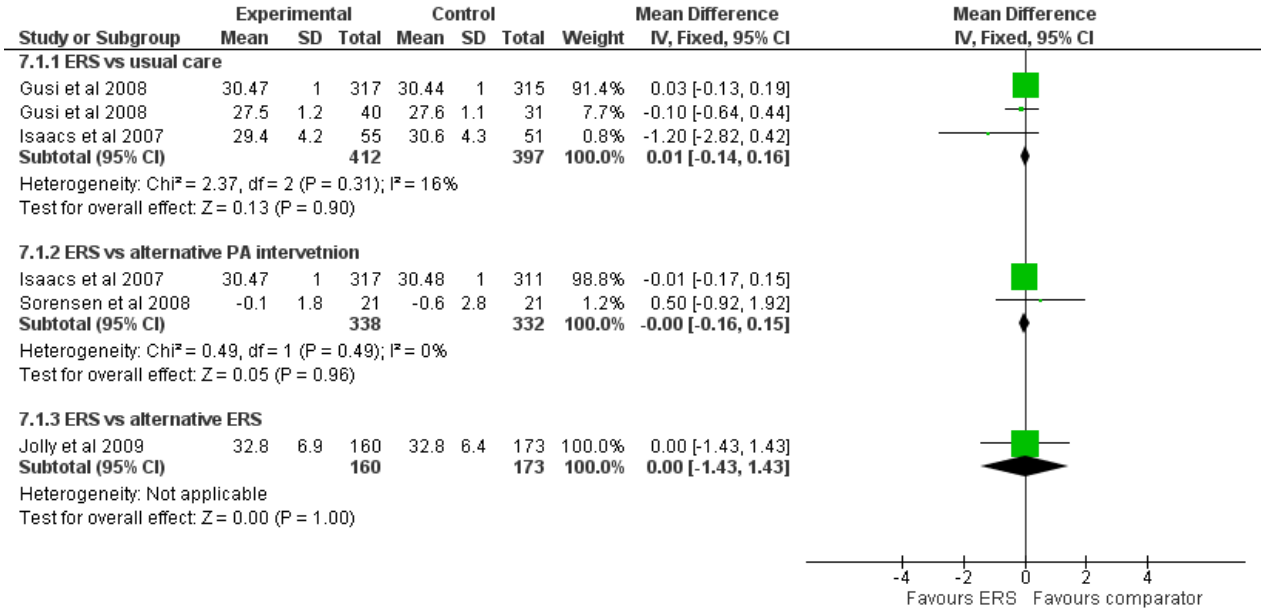


Figure 9: BMI at 6-12 months follow-up[3]



5.2.4.2 Physical Fitness

No additional data were available for this outcome, the following results are taken from Pavey *et al.*,[3] The studies by Taylor *et al.*,[11] Isaacs *et al.*,[17] and Sorensen *et al.*,[23] reported physical fitness outcomes (Table 12).

Exercise referral scheme versus usual care

Taylor *et al.*,[11] reported a lower (more favourable) submaximal heart rate (at 150 W) for ERS compared with usual care. Isaacs *et al.*,[17] reported no significant differences in any of the physical fitness measures (submaximal bike and shuttle walk, isometric knee strength, leg extension power) between the ERS and usual care groups at follow-up except at 10 weeks for the submaximal bike ergometer test. Pooling of the cardiorespiratory measures (mode: cycle ergometer or cycle/walking) showed no difference between ERS and usual care (Figure 10). There was considerable evidence of statistical heterogeneity.

Exercise referral scheme versus alternative physical activity intervention

Isaacs *et al.*,[17] and Sorensen *et al.*,[23] reported no significant differences in any of the physical fitness measures between the ERS and the alternative PA intervention groups at follow-up (see Figure 10).

Exercise referral scheme versus exercise referral scheme plus self-determination theory

The study of Duda *et al.*,[16] did not assess physical fitness.

Table 11: Summary of physical fitness data at follow-up in included ERS trials[3]

Study and time of follow-up	Mean predicted heart rate at a workload of 150W		VO2max (ml/kg/minute)		Submaximal bike ergometer (minutes)		Submaximal shuttle walk (m)		Isometric knee strength (N)		Leg extension power (W)	
	ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)	ERS, mean (SD)	Control, mean (SD)
ERS vs. usual care												
Taylor *et al.*,[11]												
16 weeks[a]	138.6 (23.0)	147.2 (29.7)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
26 weeks[a]	136.3 (22.6)	142.3 (28.5)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
37 weeks[a]	134.2 (19.0)	146.0 (24.2)[c]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Isaacs *et al.*,[17]												
10 weeks[a]	Not reported	Not reported	Not reported	Not reported	9.65 (1.5)	8.87 (1.5)[c]	456 (102)	434 (104)[b]	277 (54)	265 (56)[b]	174 (31)	165 (31)[b]
6 months[a]	Not reported	Not reported	Not reported	Not reported	8.86 (1.7)	9.08 (1.7)[b]	445 (96)	434 (97)[b]	265 (58)	267 (66)[b]	173 (66)	167 (68)[b]
ERS vs. alternative PA intervention												
Sorensen *et al.*,[23]												
4 months[a]	Not reported	Not reported	23.8 (7.1)	21.7 (11.0)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Study and time of follow-up	Mean predicted heart rate at a workload of 150W		VO2max (ml/kg/minute)		Submaximal bike ergometer (minutes)		Submaximal shuttle walk (m)		Isometric knee strength (N)		Leg extension power (W)	
	ERS, mean (SD)	**Control, mean (SD)**	**ERS, mean (SD)**	**Control, mean (SD)**	**ERS, mean (SD)**	**Control, mean (SD)**	**ERS, mean (SD)**	**Control, mean (SD)**	**ERS, mean (SD)**	**Control, mean (SD)**	**ERS, mean (SD)**	**Control, mean (SD)**
10 months[a]	Not reported	Not reported	23.0 (8.2)	22.4 (12.7)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Isaacs *et al.*,[17]												
10 weeks[a]	Not reported	Not reported	Not reported	Not reported	9.65 (1.5)	8.92 (1.7)[b]	456 (102)	437 (100)[b]	277 (54)	275 (58)[b]	174 (31)	166 (32)[b]
6 months[a]	Not reported	Not reported	Not reported	Not reported	8.86 (1.7)	8.92 (1.8)[b]	445 (96)	448 (95)[b]	265 (58)	264 (66)[b]	173 (66)	164 (68)[b]

N, newton; N/A: not applicable; SD, standard deviation; V O2max, maximal oxygen uptake; W, watt.

[a] Numbers of individuals with complete data/questionnaires.

[b] Between-group difference not statistically significant at $p \leq 0.05$.

[c] Between-group differences statistically significant at $p \leq 0.05$.

5.2.4.3 Clinical factors

Five studies provided information on clinical outcomes, i.e. CHD risk factors (Table 13), weight and obesity measures (Table 14) and respiratory function (Table 15).

Exercise referral scheme versus usual care

Taylor *et al.*,[11] reported percentage of body fat in ERS participants compared with usual care at follow-up and found no statistically significant difference between the groups. Gusi *et al.*,[30] reported a lower BMI, with no other between-group differences in weight and body fat outcomes for the other measured clinical factors (Figures 13 and 14). There was no significant difference in resting blood pressure, serum lipids or respiratory function between ERS and usual care at follow-up (Figures 11 and 12).

Exercise referral scheme versus alternative physical activity intervention

In both the studies by Isaacs *et al.*,[17] and Sorensen *et al.*,[23] there were no significant between-group differences at follow-up in resting blood pressure (Figures 11 and 12), BMI (Figure 13), body fat outcomes, serum lipids and respiratory function. The Sorensen *et al.*,[23] trial reported reduced levels of glycosylated haemoglobin (HbA1c) in both the ERS group (mean –0.26%, 95% CI –0.79% to 0.27%) and the PA counselling group (mean –0.23, 95% CI –0.47 to 0.02) at 4-month follow-up, although there was no difference between groups.

Exercise referral scheme versus exercise referral scheme plus self-determination theory

Duda *et al.*,[16] reported no significant difference between standard ERS and ERS plus SDT in body mass index (BMI) or resting blood pressure.

Table 12: Summary of CHD risk factors in included ERS trials

Study and time of follow-up	SBP (mmHg)		DBP (mmHg)		Cholesterol (mmol/l)		High-density lipoproteins (mmol/l)		Low-density lipoproteins (mmol/l)		Triglycerides (mmol/l)	
	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)
ERS vs. usual care												
Taylor *et al.*,[11]												
16 weeks[a]	130 (14.5)	130 (14)[b]	84 (8)	84 (8)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
26 weeks[a]	130 (14)	131 (14)[b]	84 (8)	84 (8)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
37 weeks[a]	130 (17)	131 (18)[b]	85 (9)	83 (9)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Isaacs *et al.*,[17]												
10 weeks[a]	133 (10)	132 (10)[b]	82 (6)	83 (6)[b]	5.68 (0.53)	5.71 (0.42)[b]	1.35 (0.18)	1.35 (0.18)[b]	3.41 (0.46)	3.44 (0.47)[b]	2.12 (0.71)	2.14 (0.71)[b]
6 months[a]	133 (12)	133 (12)[b]	82 (6)	82 (7)[b]	5.65 (0.50)	5.60 (0.50)[b]	1.37 (0.25)	1.38 (0.17)[b]	3.40 (0.48)	3.37 (0.50)[b]	2.04 (0.74)	2.00 (0.84)[b]
ERS vs. alternative PA intervention												
Isaacs *et al.*,[17]												
10 weeks[a]	133 (10)	134 (10)[b]	82 (6)	84 (6)[b]	5.68 (0.53)	5.69 (0.53)[b]	1.35 (0.18)	1.33 (0.17)[b]	3.41 (0.46)	3.45 (0.46)[b]	2.12 (0.71)	2.05 (0.76)[b]

Study and time of follow-up	SBP (mmHg)		DBP (mmHg)		Cholesterol (mmol/l)		High-density lipoproteins (mmol/l)		Low-density lipoproteins (mmol/l)		Triglycerides (mmol/l)	
	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)
6 months[a]	133 (12)	134 (12)[b]	82 (6)	83 (6)[b]	5.65 (0.50)	5.56 (0.57)[b]	1.37 (0.25)	1.37 (0.16)[b]	3.40 (0.48)	3.36 (0.48)[b]	2.04 (0.74)	1.95 (0.74)[b]
ERS vs. ERS plus SDT												
Duda *et al.*, [16]												
6 months[a]	130 (17)	127 (16)[b]	82 (11)	79 (11)[b]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

DBP, diastolic blood pressure; N/A, not applicable; SD, standard deviation.

a Numbers of individuals with complete data.

b Between-group difference not statistically significant at $p \leq 0.05$.

Table 13: Summary of weight and measures of obesity outcomes in included ERS trials[3]

Study and time of follow-up	Weight (kg)		BMI (kg/m2)		Body fat (%)		Waist-hip ratio (cm)	
	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)
ERS vs. usual care								
Taylor *et al.*,[11]								
16 weeks[b]	Not reported	Not reported	27.5 (0.6)	27.6 (0.6)[c]	70 (8)	76 (8)[d]	0.87 (0.08)	0.83 (0.09)[c]
26 weeks[b]	Not reported	Not reported	27.3 (1.3)	27.5 (1.1)[c]	70 (11)	75 (11)[d]	0.87 (0.08)	0.83 (0.09)[c]
37 weeks[b]	Not reported	Not reported	27.5 (1.3)	27.6 (1.1)[c]	71 (13)	76 (13)[d]	0.87 (0.08)	0.84 (0.09)[c]
Isaacs *et al.*,[17]								
10 weeks[e]	81 (3)	81 (3)[c]	30.2 (0.8)	30.1 (1.5)[c]	37.4 (1.9)	37.5 (1.9)[c]	0.88 (0.06)	0.89 (0)[c]
6 months[e]	82 (3)	82 (3)[c]	30.5 (1.1)	30.4 (1.1)[c]	37.8 (2.4)	37.8 (2.4)[c]	0.88 (0)	0.88 (0)[c]
Gusi *et al.*,[30]								
6 months[b]	Not reported	Not reported	29.7 (4.2)	30.6 (4.3)[d]	Not reported	Not reported	Not reported	Not reported
ERS vs. alternative PA intervention								
Sorensen *et al.*,[23]								
4 months[a]	–1.1 (4)	–1.1 (4)[c]	–0.3 (1.3)	–0.04 (1.6)[c]	Not reported	Not reported	Not reported	Not reported
10 months[a]	–0.3 (4.4)	–0.3 (4.4)[c]	–0.1 (1.9)	–0.6 (2.8)[c]	Not reported	Not reported	Not reported	Not reported
Isaacs *et al.*,[17]								
10 weeks[a]	81 (3)	81 (3)[c]	30.2 (0.8)	30.2 (1.6)[c]	37.4 (1.9)	37.1 (1.9)[c]	0.88 (0.06)	0.88 (0.06)[c]
6 months[a]	82 (3)	82 (3)[c]	30.5 (1.1)	30.5 (1.1)[c]	37.8 (2.4)	37.8 (1.1)[c]	0.88 (0)	0.88 (0)[c]
ERS vs. ERS plus SDT								
Duda *et al.*,[16]								
6 months[a]	Not reported	Not reported	32.8 (6.9)	32.8 (6.4)[c]	Not reported	Not reported	Not reported	Not reported

N/A, not applicable; SD, standard deviation.
[a] Taylor *et al.*,27 sum of four skinfolds (mm).
[b] Numbers of individuals with complete data.
[c] Between-group difference not statistically significant at $p \leq 0.05$.
[d] Between-group differences statistically significant at $p \leq 0.05$.
[e] All randomised participants.
[f] Mean change score.

Table 14: Summary of respiratory function outcomes in included ERS trials

Study and time of follow-up	FEV/FVC ratio		PEF	
	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)
ERS vs. usual care				
Isaacs *et al.*,[17]				
10 weeks[a]	0.86 (0.0)	0.86 (0.06)[b]	417 (58)	409 (58)[b]
6 months[a]	0.86 (0.09)	0.86 (0.09)[b]	407 (115)	411 (117)[b]
ERS vs. alternative PA intervention				
Isaacs *et al.*,[17]				
10 weeks[a]	0.86 (0.0)	0.85 (0.06)[b]	417 (58)	407 (61)[b]
6 months[a]	0.86 (0.09)	0.85 (0.09)[b]	407 (115)	416 (117)[b]

FEV, forced expiratory volume; FVC, forced vital capacity; PEF, peak expiratory flow; SD, standard deviation.

[a] All randomised participants.

[b] Between-group difference not statistically significant at $p \leq 0.05$.

Figure 10: Physical fitness at 6-12 months follow-up

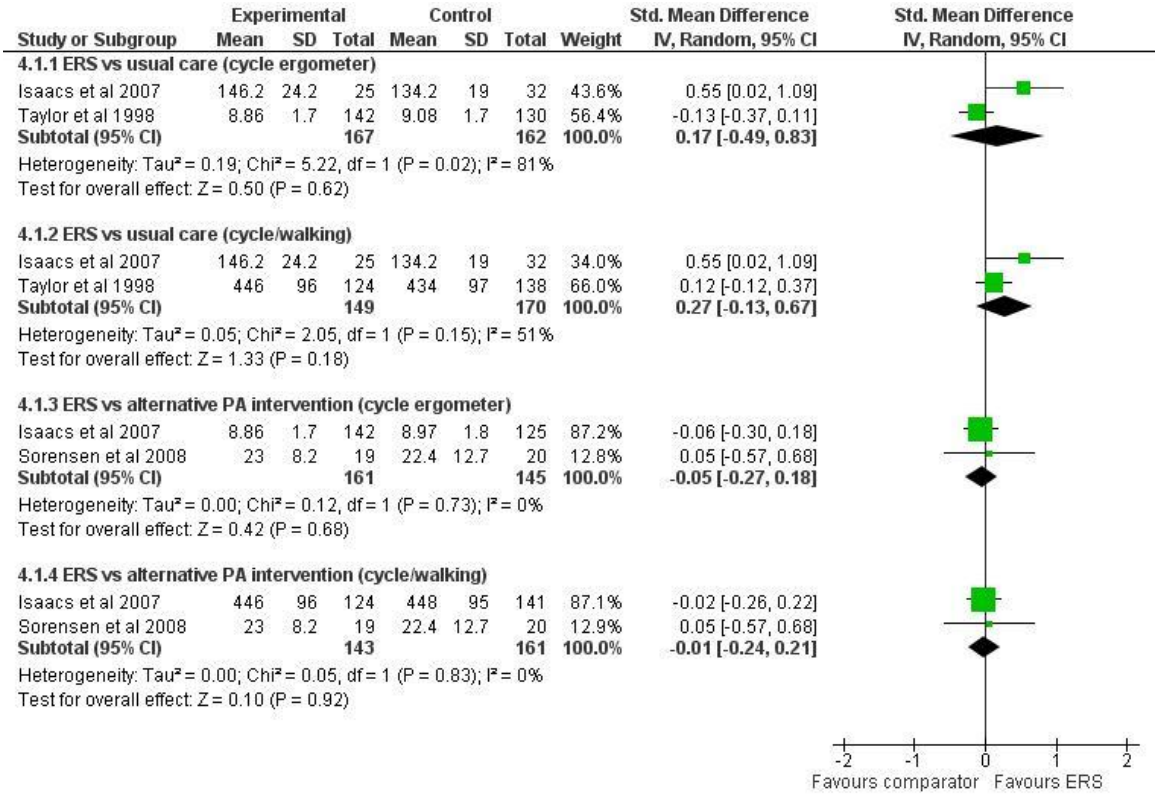


Figure 11: Systolic blood pressure (SBP) at 6-12 months follow-up[3]

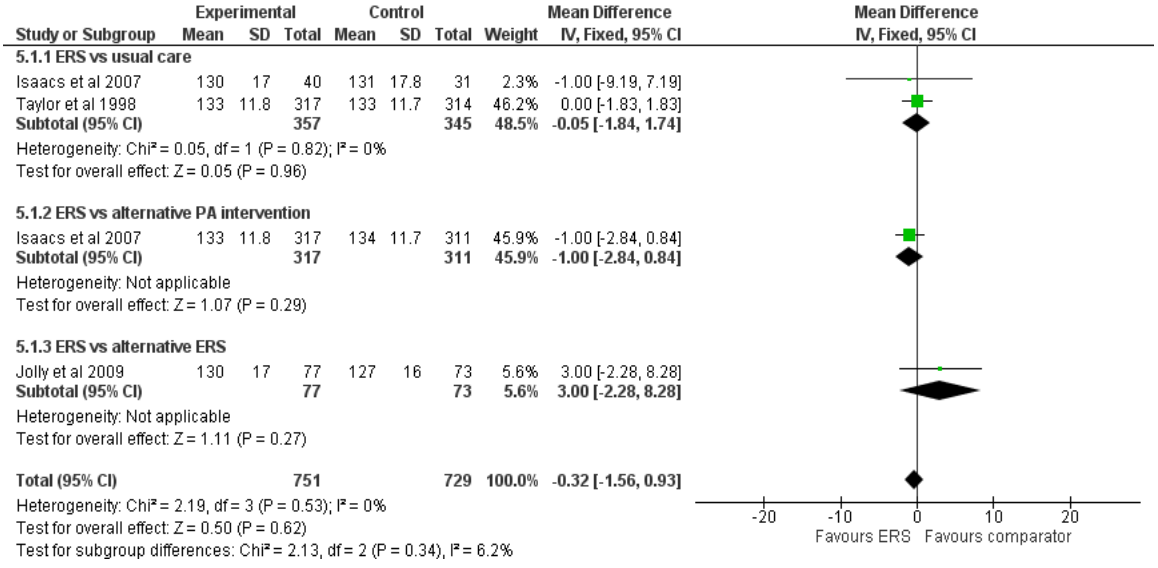


Figure 12: Diastolic blood pressure (DPB) at 6-12 months follow-up[3]

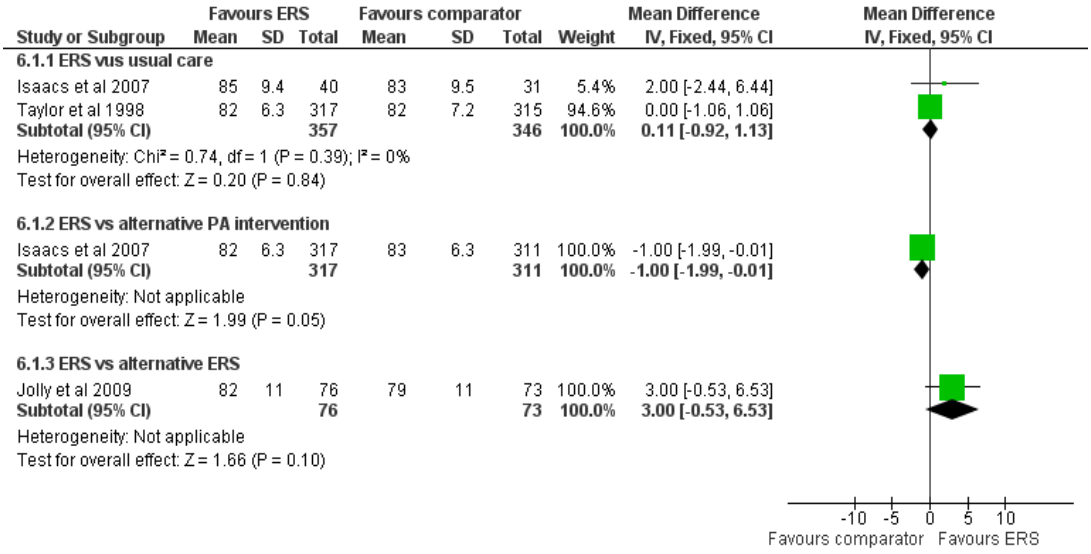


Figure 13: BMI at 6-12 months follow-up[3]

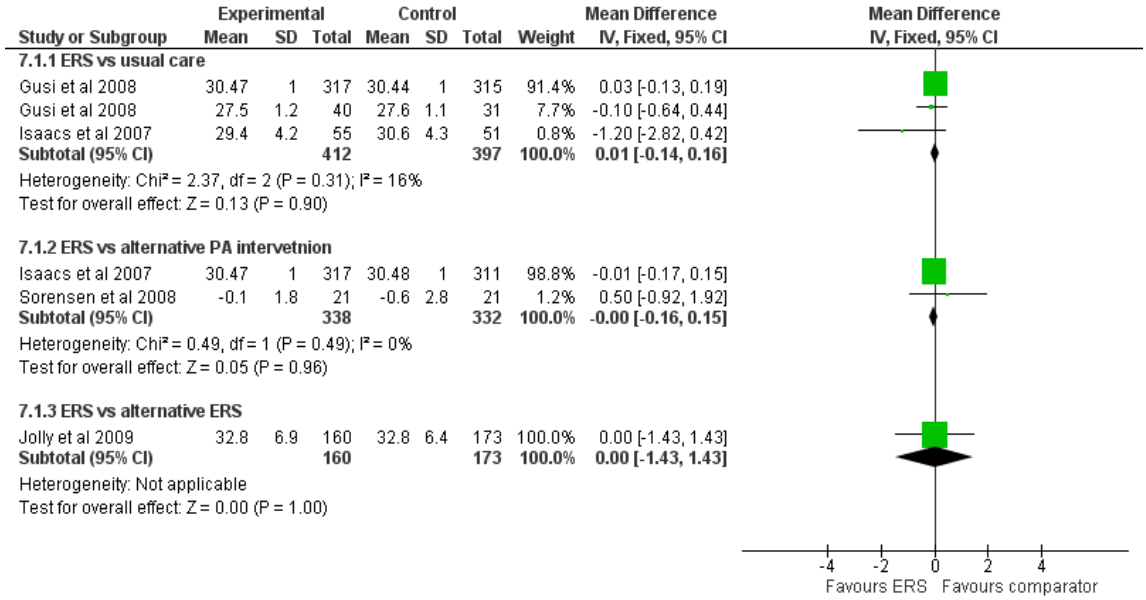
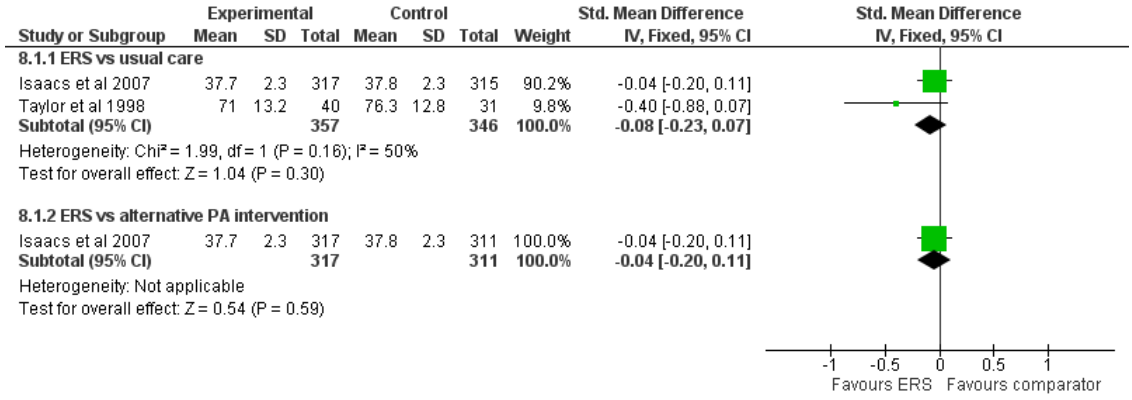


Figure 14: Body fat at 6-12 months follow-up[3]



5.2.4.4 Psychological well-being

Four studies[19,25,30,36] reported psychological well-being outcomes and the results are summarised in Table 16.

Exercise referral scheme versus usual care. Taylor and Fox[28] reported physical self-perceptions measures, with improvements shown in physical self-worth (PSW), and perceptions of physical condition and physical health collected physical self-perceptions data, and reported significant differences favouring the ERS group compared with usual care group at 16 and 37 weeks. Issacs *et al.*,[17] reported no differences between the ERS and usual care groups in the anxiety and depression scores using the Hospital Anxiety Depression Scale (HADS) at 6 months. In the Gusi *et al.*, study, all measures (Geriatric Depression Scale, State Trait Anxiety Inventory and the anxiety/depression subscale of the European Quality of Life-5Dimensions (EQ-5D)) at 6 months were found to favour ERS participants compared with those receiving the usual care. In the Murphy *et al.*, study, participants who were referred for mental health reason or in combination with CHD, there were significantly lower levels of anxiety (OR -1.56, (95% CI -2.75 to -0.38) and depression (OR -1.39, 95% CI -2.60 to -0.18), but no effect on physical activity.Murphy *et al.*,[25] also found significant interactions with gender for both mental health outcomes, with the beneficial effect of the intervention only apparent among women. There was a suggestion that the intervention was more effective on mental health outcomes among the youngest age group (18-44), although this was not statistically significant. Effects did not vary significantly by deprivation status.

Pavey *et al.,*[10] in a review updating his earlier review[3] pooled HADS data from Murphy *et al.,*[25] and Gusi *et al.,*[30] This showed a significant reduction in depression (-0.82 (95% CI: -1.28 to -0.35)) but not in anxiety (-4.12 (95% CI: -11.52 to 3.28) for exercise referral schemes compared with usual care.

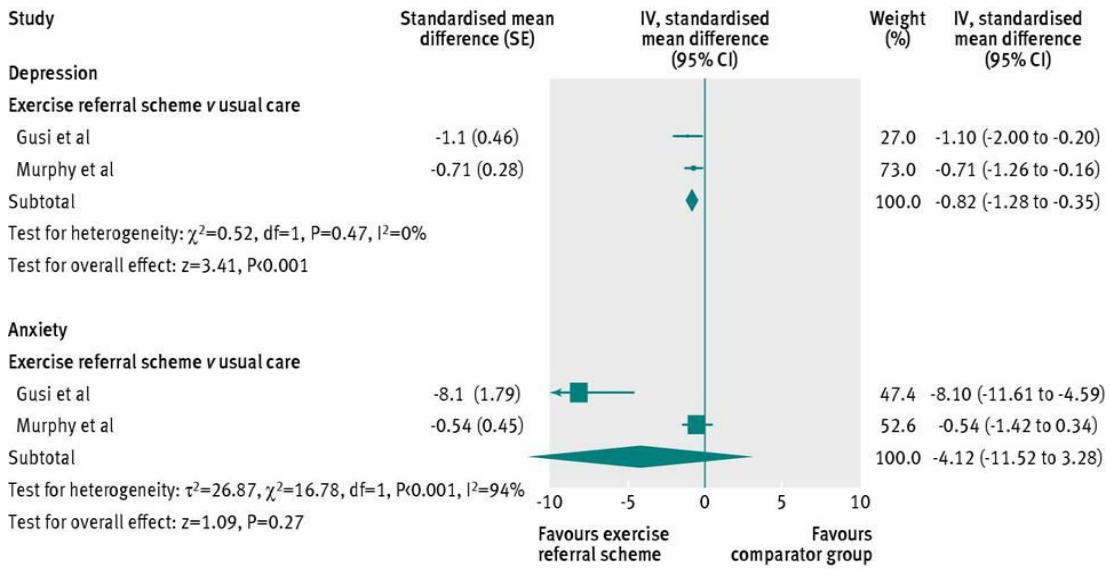
Exercise referral scheme versus alternative physical activity intervention

Isaacs *et al.,*[17] reported no differences between the ERS and walking programme in anxiety or depression outcomes at 6 months' follow-up.

Exercise referral scheme versus exercise referral scheme plus self-determination theory

Duda *et al.,*[16] reported no difference between groups in anxiety or depression outcomes at either 3 or 6 months' follow-up.

Figure 15: Meta-analysis of depression and anxiety in patients, at 6-12 month follow-up. SE=standard error. Fixed effects model used. IV=inverse variance[31]



5.2.4.4 Health-related quality of life

Five studies[19,24,25,30,32] reported HRQoL, as summarised in Table 17.

Exercise referral scheme versus usual care

Isaacs *et al.,*[17] reported no differences between the ERS and usual-care groups at follow-up on the Short Form questionnaire-36 items (SF-36) mental health scale. Gusi *et al.,*[30] observed higher EQ-5D scores in the ERS group than in the usual care group at 6 months. Murphy *et al.,*[25] also observed higher EQ-5D scores in the ERS group than in the usual care group at 12 months but it was not statistically significant.

Exercise referral scheme versus alternative physical activity intervention

Isaacs *et al.,*[17] reported no differences between the ERS and walking groups at follow-up on the SF-36 mental health scale score. Similarly, Sorensen *et al.,*[23] found no differences between the groups at follow-up on the Short Form questionnaire-12 items (SF-12) mental and physical scales.

Exercise referral scheme vs exercise referral scheme plus self-determination theory

Duda *et al.,*[16] reported no difference between groups in overall Dartmouth CO-OP chart score although there was a difference for the feelings subscale at 6 months in favour of the alternative ERS group (not tabularised).

5.2.4.5 Patient satisfaction

Three studies[13,16,19] reported patient satisfaction and results are summarised in Table 18.

Exercise referral scheme versus usual care

The Harrison *et al.,*[14] study reported that the ERS group were significantly more satisfied with the information they received and felt they needed less information about PA, compared with usual care group. In the Taylor *et al.,*[11] study, comments about the concept of ERS (measured at 8 weeks) identified that 50% of patients were positive, 35% had mixed feelings and 15% had only negative comments. Negative comments included a long waiting time before introductory session, lack of staff support, crowded facilities and inconvenient facility times.

Exercise referral scheme versus alternative physical activity intervention

In the Isaacs *et al.,*[17] study there was no between-group difference in participant satisfaction with received information or the need for additional information. In the ERS group, 97.8% felt better for taking part and enjoyed the programme compared with 93.8% feeling better for taking part and 95.2% enjoying the programme for the walking group.

Exercise referral scheme versus exercise referral scheme plus self-determination theory

Duda *et al.*,[16] did not assess participant satisfaction.

5.2.4.6 Adverse events

Although participation in ERS has the potential to lead to negative events (e.g. an increase in exercise-related musculoskeletal injuries or exercise-related cardiac complications), only the Isaacs *et al.*,[17] study assessed such events. Using GP records, the authors assessed the change in consultations before and after ERS. There was evidence of a small increase in GP visits for falls and fractures in the ERS and walking groups compared with usual care control after the start of the study (Table 19).

5.2.4.7 Health-care utilisation

No studies reported hospitalisations, primary care visits or use of medication.

Table 15: Summary of psychological well-being data at follow-up in included ERS trials

Study	PSW		Anxiety		Depression		Anxiety/depression	
	ERS, mean (SD)	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**
ERS vs. usual care								
[a]Taylor and Fox[28]								
16 weeks[b]	2.31 (0.79)	2.31 (0.67)[c]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
37 weeks[b]	2.41 (0.79)	2.42 (0.54)[c]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
[d]Isaacs *et al.,*[17]								
6 months[e]	Not reported	Not reported	6.9	7.1[f]	4.8	4.9[f]	Not reported	Not reported
Gusi *et al.,*[30]								
6 months[e]	Not reported	Not reported	14.1 (9)	22.2 (9.8)[c]	1.8 (2.3)	2.9 (2.5)[c]	1.2 (0.4)	1.5 (0.7)[c]
Murphy *et al.,*[29]			**HADS 7.82 (95 % CI 7.39 to 8.25) (n=472)**	**HADS 8.35 (7.92 to 8.77) (n=502)**	**HADS 6.14 (5.73 to 6.54) (n=471)**	**HADS 6.93 (6.53 to 7.32) (n=506)**		
ERS vs. alternative PA intervention								
[d]Isaacs *et al.,*[17]								
6 months[e]	Not reported	Not reported	6.9	7.5[f]	4.8	5.1[f]	Not reported	Not reported
ERS vs. ERS plus SDT								
Duda *et al.,* [16]								
3 months[b]	Not reported	Not reported	7.7 (4.4)[f]	8.89 (4.3)	5.9 (4.2)[f]	6.68 (4.1)	Not reported	Not reported
6 months[b]	Not reported	Not reported	7.9 (4.8)[f]	8.86 (4.7)	6.1 (4.4)[f]	6.65 (4.3)	Not reported	Not reported

SD, standard deviation. HADS: Hospital Anxiety and Depression Scale

[a] Significant difference in change from baseline between groups.

[b] All randomised participants.

[c] Between-group differences statistically significant at $p \leq 0.05$.

[d] Only mean values available.

[e] Numbers of individuals with complete data/questionnaires.

[f] Between-group difference not statistically significant at $p \leq 0.05$.

Table 16: Summary of HRQoL data at follow-up in included ERS trials

Study and time of follow-up	**SF-36 mental**		**SF-12 mental**		**SF-12 physical**		**EQ-5D**		**Dartmouth QoL (overall QoL scale)**	
	ERS, mean (SD)	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**
ERS vs. usual care										
[a]Isaacs *et al.*,[17]										
6 months[b]	54.2	54.3[c]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Gusi *et al.*,[30]										
6 months[d]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	0.89 (0.18)	0.51 (0.2)[e]	Not reported	Not reported
Murphy *et al.*,[25]										
12 months							**0.64 (0.32) (n=395)**	**0.61 (0.32) (n=391)**		
ERS vs. alternative PA intervention										
Sorensen *et al.*,[23]										
4 months[b]	Not reported	Not reported	40 (10.7)	37 (11.9)[c]	49 (1017.6)	46 (13.1)[c]	Not reported	Not reported	Not reported	Not reported
10 months[b]	Not reported	Not reported	41 (10.8)	39 (10.9)[c]	51 (11.6)	45 (15.4)[c]	Not reported	Not reported	Not reported	Not reported

Study and time of follow-up	**SF-36 mental**		**SF-12 mental**		**SF-12 physical**		**EQ-5D**		**Dartmouth QoL (overall QoL scale)**	
	ERS, mean (SD)	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**	**ERS, mean (SD)**	**Usual care, mean (SD)**
[a]Isaacs *et al.*,[17]										
6 months[b]	54.3	53[c]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
ERS vs. ERS plus SDT										
Duda *et al.*, [16]										
3 months	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	3.16 (0.8)[c]	3.25 (0.7)[c]
6 months	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	3.15 (0.8)[c]	3.24 (0.8)[c]

QoL, quality of life; SD, standard deviation.
[a] Only mean values available.
[b] All randomised participants.
[c] Between-group difference not statistically significant at $p \leq 0.05$.
[d] Numbers of individuals with complete data/questionnaires.
[e] Between-group differences statistically significant at $p \leq 0.05$ (p-value calculated by authors of the present report).

Table 17: Summary of participant satisfaction in included ERS trials

Study	Satisfied with received information (%)		Needed further information (%)	
	ERS, mean (SD)	Usual care, mean (SD)	ERS, mean (SD)	Usual care, mean (SD)
ERS vs. usual care				
Harrison *et al.*,[14]				
3 months	92	69[a]	43	54[a]
ERS vs. alternative PA intervention				
Isaacs *et al.*,[17]				
10 weeks	97	96[b]	15	17[b]

[a] Statistically significant at $p \leq 0.05$ (p-value calculated by authors of the present report).
[b] Difference not statistically significant at $p \leq 0.0$

Table 18: Adverse events reported by the Isaacs *et al.*,[17] UK study (GP visits)

Adverse events	Leisure centre	Walking control	Advice-only control
Visits for chest pain			
12–6 months before start of study	1 (%)	3	7
6 months before start of study	3 (%)	4	7
Start of study to 6 months	2 (%)	9	7
6–12 months after start of study	10 (%)	4	-
Visits for aches/pains			
12–6 months before start of study	64	48	56
6 months before start of study	62	53	55
Start of study to 6 months	52	42	44
6–12 months after start of study	63	44	-
Visits for sprains			
12–6 months before start of study	2	2	7
6 months before start of study	3	6	2
Start of study to 6 months	1	4	6
6–12 months after start of study	2	0	-
Visits for falls			
12–6 months before start of study	1	1	0
6 months before start of study	1	1	2
Start of study to 6 months	9	2	0
6–12 months after start of study	3	6	-
Visits for fractures			
12–6 months before start of study	0	1	1
6 months before start of study	0	0	0
Start of study to 6 months	1	0	0
6–12 months after start of study	0	4	-

5.2.4.8 Intervention characteristics relating to effectiveness and adherence outcomes

Since the impact of exercise referral schemes on physical activity outcomes was not significant relative to control in most studies, it is difficult to tease out the characteristics of effective interventions. The only study to find a significant (albeit small) benefit of an exercise referral scheme over and above brief advice on some physical activity outcomes utilised a counselling intervention (three sessions) based on motivational interviewing plus access to subsidised exercise classes for 16 weeks, compared with normal care and brief written information.[29] The duration of the scheme was slightly longer than most other interventions, and the components of the scheme were similar to the other interventions, apart from the use of motivational interviewing as a tool in exercise counselling (although fidelity was found to be poor). The comparison condition may have been less intensive than comparison conditions in some other studies, and interestingly levels of adherence were low.

Table 19: Comparison of included studies' intervention (and control) characteristics relative to effectiveness and adherence

Study	Scheme duration	No. of sessions per week	Duration of exercise sessions	Group or individual	Components	Theoretical basis	Control condition	Follow-up	Effectiveness	Adherence
Taylor 1998/ 2005	10 weeks	2	30-40 minutes	Group and/or individual	Exercise prescription; Subsidised exercise sessions	Not reported	HEA leaflets on preventing CHD (but no specific PA advice)	8, 16, 26 & 37 weeks	RR: 1.12 [0.80, 1.55][a] RR: 0.95 [0.63, 1.45][b]	88%
Stevens 1998	10 weeks	Not reported	NA	Not reported	Counselling	Not reported	Information on PA and health, and local facilities	8 months	RR: 1.13 [0.99, 1.30][a] RR: 1.13 [0.99, 1.30][b]	35%
Harrison 2004	12 weeks	2	1 hour	Group and/or individual	Counselling; Subsidised exercise sessions	Not reported	Written information only	6 months, 9 months & 12 months	RR: 1.27 [0.84, 1.90][a] RR: 1.23 [0.80, 1.89][b]	84%
Sorensen 2006	4 months	2 for first 2 months, 1 for second 2 months	1 hour	Group	Counselling; Supervised exercise sessions	Trans-theoretical model	Low-intensive intervention (PA counselling)	4 months & 10 months		92%
Isaacs 2007	10 weeks	2	45 minutes	Group and/or individual	Supervised exercise sessions	Not reported	Advice only (tailored PA advice, information on local facilities)	6 months & 1 year	Mean difference: 45.00 [-31.42, 121.42][c] RR: 1.19 [0.91, 1.55][a] RR: 1.05 [0.78, 1.42][b]	100%
Gusi 2008	6 months	3	50 minutes	Group	Supervised exercise sessions	Not reported	Best care in general practice (incorporating brief advice)	6 months	Not reported	
Duda2014	12 weeks	NR	NA	Group and/or individual	Counselling; Self-management booklet	Self-determination theory	Standard ERS provision	3 months & 6 months	Not reported	55.6%
Murphy 2012	**16 weeks**	**1**	**Not reported**	**Group and/or individual**	**Counselling; Subsidised exercise classes**	**Motivational interviewing**	**Normal care and brief written information**	**12 months**	**Mean difference: 58.11 [16.38, 99.84][c]** **RR: 1.10 [1.01, 1.20][a]** **RR: 1.05 [0.95, 1.17][b]**	**43.8%**

[a] Number achieving 90-150 minutes PA/week (denominators as reported) risk ratio and 95% confidence intervals
[b] Number achieving 90-150 minutes PA/week (ITT analysis), risk ratio and 95% confidence intervals
[c] Mean difference (total minutes of moderate to vigorous physical activity) [95% CI]

Table 20: Detailed description of ERS interventions reported across included studies

Study	Description
Taylor 1998/2005	Exercise prescription and 10-week programme of reduced price sessions at a leisure centre (group and/or individual)
Stevens 1998	Two consultations centred around becoming more active with a focus on what participants already did, options for becoming more active and keeping a physical activity diary (no formal exercise sessions) (group and/or individual)
Harrison 2004	Consultation at a leisure centre followed by subsidised 12-week borough-wide leisure pass; participants were encouraged to attend at least two centre-based sessions a week (group and/or individual)
Sorensen 2006	Health profiles (lifestyle and health questions) and motivational counselling (based on the Transtheoretical Model of behaviour change), followed by 4-month group-based training involving aerobic conditioning (e.g. Nordic walking and aerobics), light strength conditioning, stretching and games, with additional health profiles and motivational counselling after 2 and 7 months (group)
Isaacs 2007	Instructor-led exercise classes in a leisure centre setting (types of class available were aerobics, body conditioning, aqua-aerobics, gymnasium and an optional swimming class) and instructor-led walks (graded 1-5 on difficulty, participants could choose) (group and/or individual)
Gusi 2008	Supervised walks that consisted of walking alternating with specific exercises (joint mobility, brisk-walking, strengthening, stretching and brisk walking with foot-steps and hand-claps) (group)
Duda 2014	Consultations based on self-determination theory: initial 1-hour one-to-one person-centred interview, including optional fitness appraisal and exercise promotion booklet, then 15-20 minute face-to-face or telephone consultation at 1 month, a brief 5-minute phone call at 2 months, followed by a 20-30 minute face-to-face or telephone consultation at 3 months, including a self-management booklet centred on maintaining physical activity (group and/or individual).
Murphy 2012	Motivational interviewing – initial consultation with an exercise professional (including introduction to leisure centre facilities and goal setting), 4-week telephone contact, 16-week consultation and then an 8-month telephone contact and 12-month review, plus discounted access to one-to-one and/or group exercise classes (group and/or individual).

Summary

- An exhaustive search of electronic databases, hand-searching journals, bibliographic searches and citation searching identified 9871 titles published since 2009. Eighty full text articles were retrieved.
- This review is an update of an earlier systematic review by Pavey *et al.*,[3] This update also included the study by Murphy *et al.*,[25] This review has incorporated additional data supplied by the study authors. Further additional data has also been incorporated exploring issues of uptake and adherence.

- One additional RCT[25], Murphy *et al.,* was identified since publication of Pavey *et al.,*[3] HTA. The study author supplied additional data allowing update of the meta-analyses exploring the impact of referral to and ERS minutes of physical activity as measured using a 7day PAR, and the number achieving 90-150 minutes of physical activity per week.

- When the effectiveness of an ERS is compared with usual care group that is receiving advice only, the relative risk (RR) of achieving 90-150 minutes of physical activity per week at 6-12 months follow-up is 1.12 (95%CI 1.04 to 1.20). This is a reduction in the earlier finding by Pavey *et al.,*[3] (RR 1.16; 95% CI 1.03 to 1.30).

- The meta-analysis of minutes of total physical activity/per week at 6-12 months follow-up also showed an increase of 55.10 minutes (95% CI 18.47 to 91.73) for those in the ERS groups compared to those receiving advice only in the control groups.

- Murphy *et al.,*[25] is the largest RCT published to date and was considered at low risk of bias. It was undertaken in Wales, and its findings are highly relevant to the UK context.

- Murphy *et al.,*[25] reported that referral and participation in ERS increased physical activity significantly for those referred for CHD risk factors (OR 1.29, 95%CI 1.04 to 1.60). However, among those referred for mental health reasons, either solely or in combination with CHD, there was no difference in physical activity between the ERS and normal care participants at 12 months follow up. The effect of being in the ERS group on all referrals was an increase in levels of physical activity at 12 months, but this finding was of borderline statistical significance (OR 1.19, 95%CI 0.99 to 1.43).

- No additional new evidence is available for the impact of ERS on physical fitness, patient satisfaction, clinical factors or adverse effects.

- The only significant improvements that have been measured for people referred to ERS are in self-reported measures of physical activity. These types of measures may be vulnerable to self report bias, particularly in the absence of blinding at outcome assessment. Only two studies attempted to blind those collecting outcome data to the participants' allocated groups. There is no evidence that the interventions lead to positive changes in body fat, BMI or blood pressure.

- Subgroup analyses offer some insights into which groups of people are most like to take up and adhere to ERS. The evidence is not consistent across the trials. Those who

adhere to the scheme are most likely to increase levels of physical activity. Those with higher levels of physical activity at baseline are also more likely to increase levels of physical activity. There is also some evidence that those referred for CHD risk factors are more likely to increase their levels of physical activity.

- Despite exploring the differences between the exercise referral schemes, it was not possible to identify particular features of the interventions that promoted changes in levels of physical activity
- The cut-point for 'sedentary' seems quite high and in most studies related to not meeting physical activity guidelines, which may be problematic as it would capture those with a broad range of activity levels. Around half of the studies did not specify that it was necessary to be sedentary for referral to the scheme, which again has implications for the interpretation of the findings.
- Interventions with a theoretical basis did not provide much explicit detail on how the theory drove the intervention

5.3 Barriers and Facilitators of Referral, Uptake and Adherence to Exercise Referral Schemes

5.3.1 Quantitative Results of RCT and Observational Studies

Quantitative analyses of the predictors of uptake and adherence to ERS have been explored by Pavey *et al.,*[3] It is beyond the scope of this short report to update this element of the review. However, as new data has become available we have added this to the existing Pavey *et al.,*[3] review.

Pavey *et al.,*[3] identified five RCTs and 14 observational studies for inclusion in their review. One additional trial[25] and two observational studies[32,40] were identified for inclusion in this update, although our search for new observational data were not exhaustive.

Sample sizes ranged across studies from 30 to 6610 participants in the observational studies and from 97 to 2068 in the RCTs. Mean age ranged from 44.9 to 51.9 years across the observational studies and from 53.o to 59.1 years for RCTs. Uptake and adherence were described differently in the included studies. Uptake was defined in one of two ways: attendance at the initial consultation with the 'exercise professional' or attendance at least one exercise session.

Most studies provided a definition of adherence – completion of a set number of exercise sessions, either numerically (e.g. completed 20 sessions) or a percentage (e.g. >80% attendance). For four studies[41-44] attendance at a post ERS consultation was also required to meet the definition of adherence.

The uptake of ERS across the RCTs ranged from 35% to 100%. Murphy *et al.*,[25] had an uptake of 85% which was slightly above the pooled result (80%, 95% CI 61% to 98%)) reported in the Pavey *et al.*,[3] review. Adherence to the scheme throughout compares favourably with the pooled rate of 37% (95%, CI 20% to 54%)) across schemes assessed by trials in the review.

Levels of uptake to ERS ranged from 28% to 81% in the observational studies and adherence ranged from 12% to 70%. The data from two additional studies[39,40] reported adherence levels of 58% and 54%.

Table 21: Summary of uptake and adherence to ERS levels across studies

Study	Uptake	Adherence	
	% (n/N)	% (n/N of patients who took up ERS)	% (n/N) of patients who were referred to ERS
RCTs			
Taylor *et al.*,[11] UK	88% (85/97)	28% (24/85)	25% (24/97)
Stevens *et al.*,[27] UK	35% (126/363)	Not reported	Not reported
Harrison *et al.*,[14] UK	84% (232/275)	Not reported	Not reported
Isaacs *et al.*,[17] UK	92% (293/317)	45% (133/293)	42% (133/317)
Sorensen *et al.*,[23] UK	100% (28/28)	Not reported	Not reported
Murphy *et al.*,[25] UK	**85% (919/1080)**	**51% (473/919)**	**Completed 16 weeks 43.8% (473/1080) Partial attendance 41.3% (446/1080)**
Observational studies			
Damush *et al.*,[33] USA	28% (113/404)	Not reported	Not reported
Dinan *et al.*,[34] UK	89% (216/242)	82% (178/216)	74% (178/242)
[a]Dugdill *et al.*,[3] UK	B: 68% (1825/2696)	A: 34% (336/958) B: 46% (849/1829)	B: 32% (849/2698)
Edmunds *et al.*,[35] UK	Not reported	51% (25/49)	Not reported

Harrison *et al.,*[14] UK	79% (5225/6610)	Not reported	Not reported
Jackson *et al.,*[36] UK	Not reported	70% (466/686)	Not reported
Jones *et al.,* [37] UK	78% (119/152)	65% (77/119)	51% (77/152)
Lord and Green[38] UK	60% (252/419)	31% (77/252)	18% (77/419)
Martin and Woolf-May[39] UK	Not reported	12% (60/490)	Not reported
Morton *et al.,*[40] UK	Not reported	40% (12/30)	Not reported
Roessler and Ibsen[41] Denmark	Not reported	70% (811/1156)	Not reported
Sowden *et al.,*[42] UK	58% (3565/6101)	39% (1404/3565)	23% (1404/6101)
James *et al.,*[52] UK	Not reported	57% (750/1315)	Not reported
[b]Gidlow *et al.,*[43] Crone *et al.,*[44] James *et al.,*[45] UK	66% (1930/2908)	48% (931/1930)	32% (931/2908)
Tobi *et al.,* UK	**Not reported**	**58% at 13 weeks (407/701) 45% at 20-26 weeks (315/701)**	**Not reported**
Hanson *et al.,* UK	**81%(1811/2233)**	**53.5% at 12 weeks (968/1811) 42.9% (777/1811) at 24 weeks**	**43.3% (968/2233) at 12 weeks 34.8% (777/2233) at 24 weeks**

[a] Two schemes evaluated: schemes A and B.
[b] Average of the three publications.

5.3.1.1 Demographic factors

Four studies[25,40,41,44] found that women were more likely to take up ERS than men, but two studies[16,45] found no association between gender and uptake. The data for adherence however, are less consistent, with one study[46] reporting that men are more likely to adhere to ERS than women and in another, that women are more likely to adhere to ERS.[40] Increasing age was a factor that strongly predicted for both, uptake of ERS and adherence to the scheme in six studies.[4,29,39,40,44,45]

Three studies found no such association.[19,41,46] Three studies[29,40,45] found that those most deprived were less like to take up ERS and two studies[29,40] found that deprivation was a predictor for not adhering to ERS. Two studies[16,44] found no such association with take up. Car ownership[25] was also a predictor both for uptake and adherence to ERS. Living in a rural location was also found

to be associated with less likelihood of uptake.[43] Two studies[39,46] found no association between ethnicity and uptake, and one found no association with adherence.[32] Those most active at baseline were also most likely to take up and to adhere to ERS.[46]

Tables 22, 23 and 24 describe the factors that have been associated with uptake and adherence in the included studies.

5.3.1.2 Medical diagnosis

The evidence for the role of medical conditions at baseline in influencing both uptake and adherence are not consistent across the studies.

Harrison *et al.,*[14] found that those with mental health problems, were more likely to take up ERS than those with no specified referral reason (OR 1.70, 95% CI 1.24 to 2.39). Gidlow *et al.,*[43] found that those with mental health problems were less likely to take up ERS than those referred with cardiovascular disease (OR 0.33, 95% CI 0.27 to 0.57). Gidlow *et al.,*[43] and Moore *et al.,*[46] both found that those with mental health conditions were less likely to adhere than those referred for other reasons. (Gidlow *et al.,*: 22% vs. 34%; Moore *et al.,* OR 0.57, 95% CI 0.43 to 0.75).

Harrison *et al.,*[14] found that the response to referral for respiratory problems was associated with deprivation, with those most deprived less likely to take up ERS than those least deprived. (OR 1.45, 95% CI 1.06 to 1.99).

Participants referred due to overweight or obesity were found to be less likely to take up the intervention[43] (0.63, 95% CI 0.50 to 0.81) or to adhere[40] to the intervention than those without these problems. However, this factor was not significant in two other studies[13,29]

Those referred with musculosketal or orthopaedic problems were also less likely to take up ERS (Gidlow *et al.,*[43] 0.75, 95% CI 0.58 to 0.99). Tobi *et al.,*[32] also found that they are less likely to adhere to ERS when compared with participants with metabolic conditions (OR 0.25; 95%CI 0.07 to 0.94).

Participants referred with CHD risk factors were also found to have lower odds of adhering than those with metabolic conditions.[32] (OR 0.18; 95% CI 0.05 to 0.70).

Sowden *et al.,*[42] reported that patients with diabetes were less likely to adhere to an ERS (OR 0.76; 95% /CI 0.63 to 0.93) than those with CVD (1.22; 95% CI 1.03 to 1.45) when compared with those without either condition.

5.3.1.3 Psychosocial

Pavey *et al.,*[3] reports the results of three studies[47-49] that assess the psychosocial predictors of adherence. Morton *et al.,*[40] found participant self-determination to positively predict ERS adherence, whereas Edmunds *et al.,*[35] found no such association. An expectation for change in personal development was also found to be positively predictive of ERS adherence.

Table 22: Summary of analysis of predictors of ERS uptake

Variable											No. of studies on this factor	+	-	No Sig assoc
	Harrison *et al.,*	Sowden *et al.,*	Gidlow *et al.,*	Damush *et al.,*	**Murphy *et al.,***	**Tobi *et al.,***	**Hanson *et al.,***	Lord & Green *et al.,*	Dugdill *et al.,*	Isaacs *et al.,*				
Sample size	6610	6160	2958	404	2068	701	2233	419	2696	317				
Uptake														
Factor														
male	0		0											
female	0	+	0		+		+	+			6	4		2
Increasing age		+	+	0	+		+	0	+	0	8	5		3
deprivation	0	0	-		-		-				5		3	2
Car ownership					+						1	1		
Rural living			-								1		1	
ethnicity				0		0					2			2
CHD risk	+				+									
Mental Health illness	+		-		-									
Overweight/ obesity			-		0	0					3	1		2
Leisure site		0					+				2	1		1
Clinic location				0										
Referral by cardiac rehab nurse							+				1	1		
Referred by GP			-								1		1	

Table 23: Summary of analysis of predictors of ERS adherence

Adherenece	Harrison *et al.,*	Sowden *et al.,*	Gidlow *et al.,*	Damush *et al.,*	**Murphy *et al.,***	**Tobi *et al.,***	**Hanson *et al.,***	Leijon *et al.,*	Lord & Green *et al.,*[38]	Dugdill *et al.,*	Isaacs *et al.,*	No. of studies on this factor	+	-	No Sig assoc
Factor															
male				-	+							2	1	1	
female							+	0				2	1		1
Increasing age					+	+	+	+				4	4		
deprivation					-		-					2		2	
Car ownership					+							1	1		
Moderately active					+							1	1		
Inactive at baseline								-				1		1	
Rural living															
ethnicity						0						1			1
CHD risk					+	-						2	1	1	
Mental Health illness					-							1		1	
Overweight/ obesity					+		-					2	1	1	
Leisure site							+					1	1		
Home based activities								+				1	1		
Referral by cardiac rehab nurse								+				1	1		

Table 24: Summary of analysis of psychosocial factors that predict adherence

Psychosocial factors	Edmunds *et al.,*	Jones *et al.,*	Morton *et al.,*	No. of studies on this factor	+	-	No Sig assoc
Stage of change		0		1			1
Self-efficacy		0		1			1
Expectations of change (health and fitness)		0		1			1
Expectations of change (personal development)		+		1	1		
Psychological well being		0		1			1
Need satisfaction	0			1			1
Perceived autonomy	0			1			1
Support	0			1			1
Self-determination			+	1	1		

5.3.2 Qualitative evaluation of the Discussion Sections of Included studies

In order to explore a further source of data to improve understanding of the factors that will influence the uptake of and adherence to exercise referral schemes, we undertook a qualitative analysis of the discussion and conclusion sections of the included studies. Often authors will report their perceived reasons for success and failure of interventions. These may not be reported in the measureable outcomes described within the results sections of published papers and these views can give valuable additional insights that are particularly relevant to the studies included in the review.

As a result of this analysis we created a logic model to summarise and describe the complexity of factors that might impact on referral to ERS, uptake, adherence and sustained change in levels of physical activity.

Factors that impact on the patterns of referral to Exercise Referral Schemes

Crucial to the success of exercise referral programmes is ensuring all those who might benefit are referred. This was identified in a number of the studies as an area which impacted on intervention effectiveness. Where researchers were involved in supporting the referral process, referral rates improved. Low referral rates were reported in studies where only one GP was involved in making referrals and in pragmatic 'real world' studies.[30-32]

Factors that were perceived to reduce health professionals' referral to exercise referral schemes was when there was a lack of enthusiasm for the project, poor knowledge of the scheme, poor interpersonal skills on behalf of the health professional.[11] Workload and competing demands and the extra time needed to make the referral were also considered barriers to referral.[27] There was also a view that certain characteristics of individuals might influence the likelihood of referral. Being younger appeared, in one study, to reduce the likelihood of being referred.[17]

There were elements of the referral process itself that were perceived as barriers to successful implementation of an ERS. This included an invitation that was non-judgmental in its tone. Other aspects of the invitation which were more likely to lead to a positive response included issuing invitations with a specific time. Where invitations required participants to make the appointment, there was poorer response to the referral.[27]

An area where there is uncertainty about potential factors that might influence referral and response to referral is in the use of cold calling by health professionals as an alternative to the GP referring following a consultation.[11] There may also be a potential role for peers in the process of referral and uptake that is as yet unexplored.[30]

Factors that Influence Uptake of Exercise Referral Schemes

A number of characteristics of the intervention were described as being factors that might shape the uptake of exercise referral schemes and adherence to the programme. The attractiveness and appeal of the intervention was felt to be important, particularly in targeting these to the individuals most likely to benefit from the intervention.[17] Using an existing scheme was also felt to be advantageous.[11] The incorporation of motivational counseling, ongoing professional support and the quality of that counseling and support were considered important factors. Another element of motivational interviewing related to the fidelity of the intervention, with poor delivery compromising the effectiveness of the intervention.[46] Interventions that had tailored motivational strategies were seen as more like to be taken up and adhered to than ones where there was a lack of choice. Schemes where support was given in a nonjudgmental way were considered important.[46] The speed of referral was considered important, with congestion in the system a barrier to uptake.[11]

There were aspects of ERS design where further research was recommended to establish their value; this included the use of telephone calls to prompt attendance, follow up sessions outside of the scheme and the additional of motivational counseling.[13,19,31]

A further barrier to uptake in trials of ERS was that some participants did not want to be randomised.[23]

Factors influencing adherence and sustained change in physical activity levels

A number of factors, relating particularly to the environment were considered important in maintaining adherence to the programme and in maintaining levels of physical activity. These included perception of the environment, and linked to this, the presence of parks and green spaces in the urban environment.[17] An environment that is not, or is not perceived to be conducive to changing levels of physical activity is a barrier to sustained behaviour change. Programmes that

included strategies to make gradual small changes, and move to levels of moderate activity, rather than interventions that promote more intense levels of physical activity were felt to have greater appeal and more likely to promote adherence and sustained change.[27]

A range of characteristics of participants also were reported to make a difference to their response to exercise referral schemes. Individuals who smoked were less likely to adhere to exercise referral schemes.[11] The evidence for people with obesity were more varied, with one study finding that those with obesity were more likely to take up the intervention and adhere to it that non-obese participants[11] and another finding the opposite.[17] More research might identify what features of the intervention made it attractive or less attractive to people with obesity. Participants with greater pre-existing levels of PA were more likely to adhere to the intervention.[13,25] One paper raised the suggestion that those volunteering to participate may have already been motivated to become (more) active.[23] Along with reports that there were fewer referrals from more deprived wards,[17] this also raises the possibility that as an intervention, it may serve to increase inequalities in health.

Additional questions

A number of questions were identified in the included studies. These included; a need to understand the needs of particular groups, to understand why people withdraw from exercise referral schemes, and the potential value of additional home support.[16,19,25]

The value of advice

Several studies explored the reasons why the intervention was not effective, when compared to advice only groups (usual care).[16,19,32] One reason was that physical activity levels also increased in the control groups who were receiving advice about the benefits of physical activity but were not referred to an ERS. The reasons why advice works in the context of these trials, where individuals are 'deprived' of the intervention, warrants further exploration.

5.3.3 Qualitative Sibling studies

We searched for qualitative studies that were undertaken as part of a mixed methods evaluation of an exercise referral scheme included in this review.

One study[25,27-29] undertook a mixed method process evaluation, using structured observation, implementer interviews and routine data to assess the extent to which the exercise referral scheme was implemented as intended. Semi structured patient interviews explored processes of change and the emergence of social patterning in responses to the scheme. (Moore *et al.*,).

The features of the intervention were as follows:

Motivational interviewing – initial consultation with an exercise professional (including introduction to leisure centre facilities and goal setting), 4-week telephone contact, 16-week consultation and then an 8-month telephone contact and 12-month review, plus discounted access to one-to-one and/or group exercise classes (group and/or individual).

The intervention recruited participants who were sedentary and had to have at least one CHD risk factor of suffer a mental health problem (mild anxiety, depression or stress).

The findings of the semi structured patient interviews are summarized below:

Qualitative study component: patient experiences of the Exercise Referral Scheme

1) Entering the scheme: routes into ERS and motivations for attendance

   Some patients described entering the ERS because their health professional had advised them to. However, others described initiating referral themselves through asking their doctor to refer them, having made an independent decision to become more active. In some centres, a majority of patients were referral seekers, with some commenting that health professionals had been unaware of the scheme until made aware of it by patients. Those who actively sought referral often had been previously active, but in many cases this had been interrupted. Joining the ERS became a way of overcoming barriers to becoming active once again.

   Patients cited various motivations for attendance, including physiological improvements, such as reduced blood pressure and weight loss. Both referral seekers and those advised to attend commonly also linked behaviour change to personal values such a as playing a pro-active role in treating and preventing illness. Older patients emphasised maintenance of autonomy and ability to perform everyday activities as principal motivators for attendance. For younger patents, however, primary motivations centred around maintaining occupational functioning or returning to work, with many having attended due to injuries or illness which prevented, or threatened to prevent them from working.

2) Experiences of ERS: Those who attended the ERS for several weeks were beginning to perceive progress towards their goals. Some mental health patients highlighted valued improvements in mood and increased social contact. Others highlighted medical improvements, such as reduced breathlessness and blood pressure, increased mobility or reduced pain. Lack of weight loss was a disappointment for several participants.

   The expertise of the professionals and the support they offered was clearly an aspect of the interventions that was valued, particularly in helping participants as they became familiar with using exercise equipment, and knowing the extent to which they should exert themselves. The professional's role in monitoring progress and promoting further progression was also valued.

   The lack of variety in the forms of exercise enabling progression was a negative element of the intervention for some who were at the later stages of the programme. The limited number of centres where the scheme was offered was potentially a barrier to participation, particularly as it relied on access to a car. Access was also more problematic for those who were working and were more constrained by time.

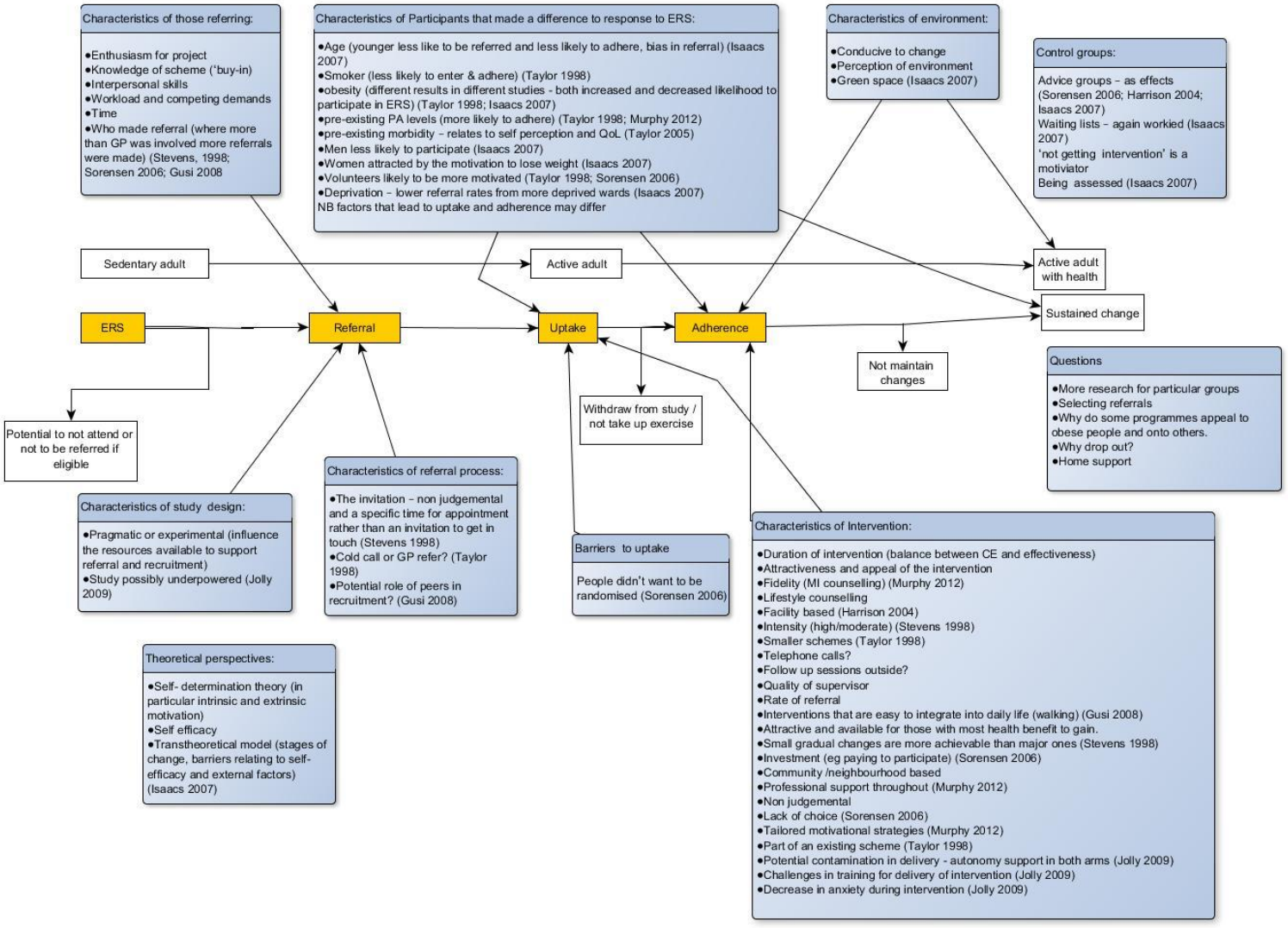
Peer support and the value of shared experiences with other patients was a positive element of the intervention, meaning that individuals felt that they would be viewed with empathy. Mixing with others who were at later stages in the programme provided positive role models. This made the exercise environment less intimidating and more supportive which encouraged participants.

3) Leaving ERS: the transition to independent activity. Some patients identified clear plans for how they would maintain increases in physical activity, sometimes having identified exit route classes they planned to enter, or focusing upon a desire to return to former hobbies. Such patients were most commonly those with a prior history of activity, some of whom had entered ERS as a means of overcoming the refusal of gyms to accept them as members.

For others, perhaps more dependent on the program to provide ideas for long-term maintenance or activity, were unsure how they might maintain change. In some cases, formation of action plans appeared to have been hampered by a lack of information about available options after the programme. Some expressed concerns that without a commitment to an agreed time and place other aspects of daily life would crowd out time for physical activity, with ERS providing justification for taking time out from other commitments, but this time becoming harder to protect after programme completion.

There were some differences in views between those at the early stages of the programme and those nearing the end of the programme. For those at the early stage, they expressed concerns regarding their ability to maintain increases without ongoing motivational and informational support from the professional. For those near the end of the programme there were perceived challenges including the loss of social support they gained while participating in the programme. The support element of having others to exercise with was an important factor in maintaining levels of physical activity. For some, there were concerns about moving into mainstream exercise settings and for some the cost of remaining active once the programme discount was withdrawn.

Figure 16: Logic Model



Logic Model demonstrating contextual factors that will shape uptake, adherence and sustained behaviour change as a result of ERS. Data derived from qualitative analysis of the discussion sections in in the included RCTs

Summary

- ERSs are ‘complex interventions’ therefore what works in one setting may not mean the intervention will necessarily work in another. It is therefore important to understand ‘what works, for whom and in what circumstances.
- When considering uptake and adherence, issues relating to who is referred and also maintenance of physical activity at the end of the intervention need also to be considered.
- A range of factors can influence who is referred to an ERS, including the support for referral, ‘buy-in’ by GPs and preconceived perceptions about patients by health professionals.
- A range of characteristics can shape how participants respond to referral. These include age, pre-existing levels of physical activity, obesity. The nature of the invitation to an ERS can also shape response from potential participants.
- ERS vary in many ways, including, professional running scheme, group based or individual sessions, incorporation of motivational counselling. They will also vary in duration of contact and length of time in scheme. There is uncertainty which elements of these schemes may have benefits for which groups. Some suggestion that group based work can be beneficial in promoting peer support. This in turn can promote sustainable change. It can put some individuals, particularly men and older people and overweight individuals who may feel more uncomfortable in group settings.
- Perceptions of the environment and the presence of ‘green space’ supports sustained change.

6. ASSESSMENT OF COST-EFFECTIVENESS

6.1 Background to independent economic assessment

In 2011, Anokye *et al.,* published the results of a cost-effectiveness model of ERS based on data from a systematic review of the effectiveness of ERS by Pavey *et al.,*[10,19] They concluded that ERS is associated with a modest increase in lifetime costs and benefits and that the cost-effectiveness of ERS is highly sensitive to small changes in the effectiveness and cost of ERS and is subject to some significant uncertainty mainly due to limitations in the clinical effectiveness evidence base.

This model was later amended to inform the NICE Public Health appraisal of brief advice (BA) in primary care to promote physical activity (PH44).[47] This latter model differed from that used by Pavey *et al.* in terms of both the model structure and its data inputs (see 6.1.6 for a comparison of these two models).

The scope for the economic analysis of ERS for this brief report was to update the Anokye *et al.,* brief advice model with evidence from an updated systematic review on the effectiveness of ERS and to update the costs.[47]

The economic analysis has therefore focused on updating only three groups of parameters and all other parameter values have remained unchanged. Firstly, estimates of the relative clinical effectiveness of ERS versus no ERS have been updated using the results from the updated systematic review given that the review identified new evidence (section 5.2 of this report). Secondly, costs were inflated to 2013 values using Personal Social Services Research Unit inflation indices.[48] Thirdly, the starting age has been set at 50 which is the mean age from the studies from which the effectiveness data has been taken. No other model parameter values were updated and the model structure remains unchanged.

There are several benefits to using an existing cost-effectiveness model to assess the cost-effectiveness of ERS. Firstly, it builds on the existing evidence base already incorporated within the model allowing resources to be focused on identifying and incorporating any new effectiveness evidence. Secondly, the repeated use of the same model across multiple NICE Public Health Appraisals is likely to increase internal consistency within the NICE process. Conversely, the lack of a *de novo* approach does limit our ability to explore alternative model structures and evidence sources. In this case, the use of an existing model was determined to be

the best option given the resources available and the model to be used was specified a-priori in our protocol.

6.1.1 Methods

Population, intervention and comparator

The population, intervention and comparator are the same as those defined in Section 3 of this report.

6.1.2 Horizon and perspective

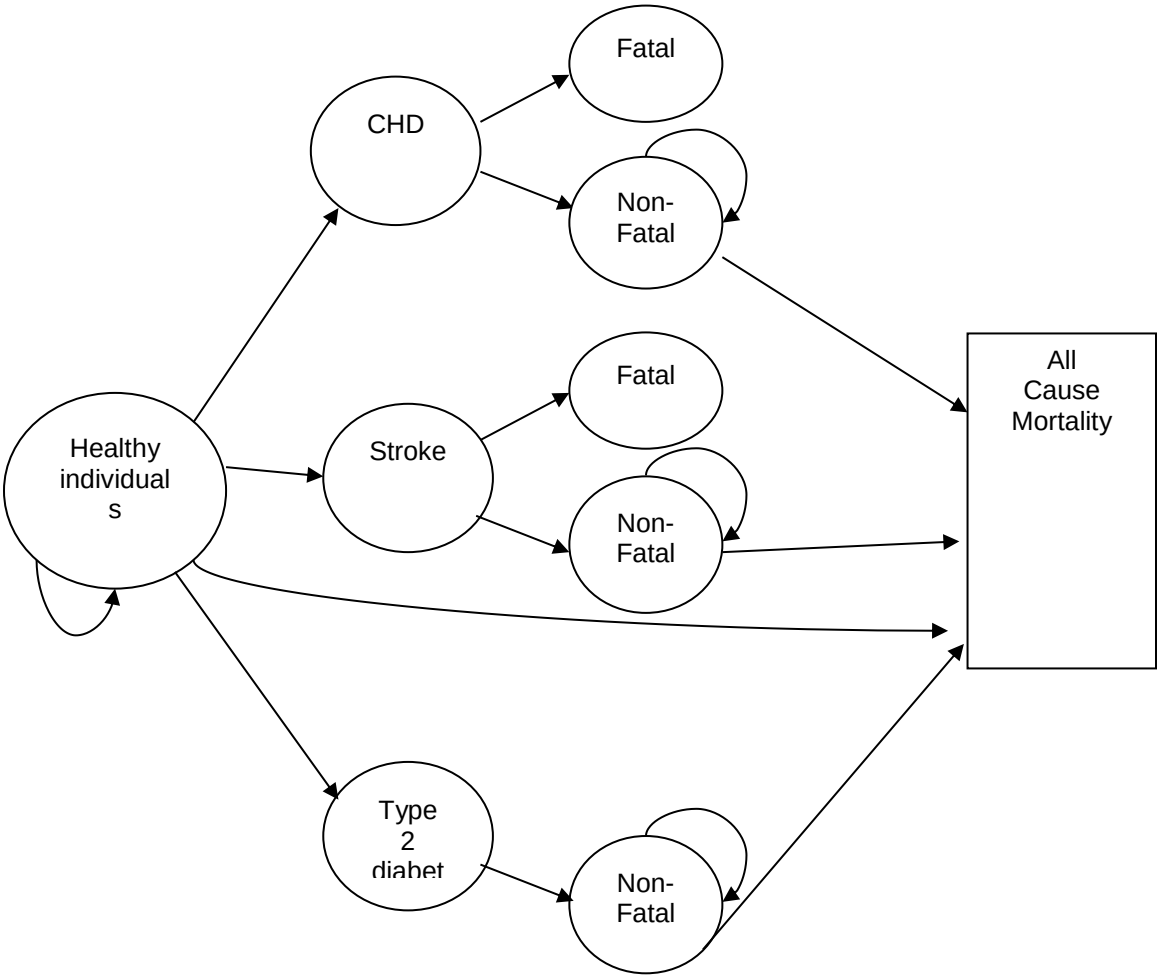
The analysis was conducted for a hypothetical cohort of 100,000 patients with a mean age of 50 years receiving either exercise referral or usual care. A lifetime horizon was adopted in order to capture the potential long-term benefits and cost savings associated with physical activity. Mean life expectancy was based on UK interim life tables and the analysis did not consider males and females separately. The economic perspective of the model is the NHS and PSS in the UK. Costs and health benefits were discounted at an annual rate of 1.5% as recommended by the Methods for the development of NICE Public Health Guidance.[49]

6.1.3 Model structure

The model structure is described in full elsewhere but we provide a brief description here.[47] The model has a Markov structure and considers a cohort of individuals aged 50 years who present in a physically inactive state and are given a referral to a service designed to increase physical activity that includes a physical activity or exercise programme compared to a control group with no referral to an exercise service. The age of the population was selected to reflect the populations enrolled in the studies providing evidence on the effectiveness of ERS.[10,29] The model estimates the likelihood of becoming physically active and the consequent risk reduction this has on coronary heart disease (CHD), stroke and type 2 diabetes mellitus.

In the first year of the model individuals either enter an 'inactive, healthy state' or an 'active, healthy' state, this is considered a 'run-in' period where individuals reach a stable level of activity. From year two and onwards, a proportion of individuals transit from the initial state into one of the following states; Event free, CHD, stroke and Type 2 diabetes. Stroke and CHD are then sub-divided into non-fatal and fatal. Patients can also die from other causes. Figure 17 shows the model structure.

Figure 17: Model structure from year 2 onwards



Key assumptions:

- Once an individual enters a disease health state they either remain in that state or die; there is no subsequent transition to other disease health states.
- Physical activity has health benefits via reduced risk for CHD, stroke and type 2 diabetes.
- Individuals with CHD, stroke and type 2 diabetes have an increased age specific all-cause mortality rate, compared with the healthy population.

6.1.4 Model parameters

Effectiveness of ERS versus usual care

The evidence for the effectiveness of ERS versus usual care is based on the results of the systematic review described in Section 5 of this report. The review identified one new study by Murphy *et al.*,[25] This study conducted a large randomised controlled trial with 2,160 participants, randomised to receive ERS or usual care. A full description of the study can be found in Section 5 of this report. This study was combined in a meta-analysis with the studies identified by Pavey *et al.*, The RR of the number of individuals becoming active versus being inactive due to ERS was 1.12 (95% CI 1.04, 1.20). This RR was calculated using the number of participants with study data at 12 months. A sensitivity analysis was also conducted using the RR estimated when taking an ITT approach (RR 1.08, 95%CI 1.00 to 1.17).

The effect of physical activity on disease outcomes

Evidence of the effect of physical activity on the development of CHD, stroke and type 2 diabetes was derived from a reference search of papers included in five national and international guideline reports that set out the science-based guidance on physical activity, fitness, and health for the UK, USA and Canada, (see Appendix 6 of Anokye *et al.*,[47]).

The RR estimate for developing CHD (non-fatal and fatal), stroke (non-fatal and fatal), and diabetes were selected from Hu *et al.*,[50,51,52] respectively. These RR estimates were based on cohort follow up periods of 19 years for CHD and stroke and 12 years for diabetes. The model applies these RR estimates for the initial 10 year period only on the assumption that it would be unrealistic for them to be applied after the follow up period.

Physical Activity habits can be quite changeable. The impact of changing habits is incorporated in the cohort relative risk estimates for the disease conditions. The studies used followed up the same people (who were either active or inactive at baseline) for a number of years, during which time some of the inactive people might have become active or vice versa, diluting the observed relationships between activity and outcomes.[58-60] Hence the protective effect of activity is assumed to last for the period in which these people were followed i.e. 10 years.

The physical activity levels and study population used to measure the effect of activity on disease outcomes were similar to those of the effectiveness estimate.

Table 25: RR estimates for developing the disease conditions

Disease conditions	RR(95% CI)	Source
CHD	0.9 (0.83,0.99)	Hu *et al.*,[50]
Stroke	0.86 (0.79,0.93)	Hu *et al.*,[51]
Diabetes	0.67 (0.53,0.84)	Hu *et al.*,[52]

Baseline risk of developing the disease conditions

The baseline risks for developing CHD, and stroke were based on age-specific UK annual incidence rates used in a NICE technology appraisal of statins and the model developed as part of the update of the NICE guideline on hypertension.[53,62,63] In these models, data were obtained from the Bromley Coronary Heart Disease Register and the Oxfordshire Community Stroke project. The baseline risk for diabetes was taken from age-specific UK incidence rates for type 1 and type 2 diabetes from 1996 to 2005 estimated in Gonzalez *et al.*,[54] Table 26 shows the baseline risks for the disease conditions in the general population.

Table 26: Baseline risks for CHD, stroke and diabetes per annum

Age	**CHD**	**Stroke**	**Diabetes**	**Source(s)**
33-34	0.000035	0.00008		Ward *et al.*,[53,55] (NCGC)[56]
(33-39)			0.00009	Gonzalez *et al.*,[54]
35-44	0.000465	0.00023		Ward *et al.*,[53,55,56]
(40-49)			0.00028	Gonzalez *et al.*,[54]
45-54	0.002095	0.00057		Ward *et al.*, (2005, 2007)[56]
(50-59)			0.000632	Gonzalez *et al.*,[54]
55-64	0.00631	0.00291		Ward *et al.*, [53,62,63]
(60-69)			0.001005	Gonzalez *et al.*,[54]
65-74	0.0097	0.0069		Ward *et al.*, (2005, 2007)[56]
(70-79)			0.001116	Gonzalez *et al.*,[54]
75-81	0.0097	0.01434		Ward *et al.*,[53,55,56]
(80-81)			0.001116	Gonzalez *et al.*,[54]

The derivation of the probabilities for developing CHD, stroke, and diabetes used in the model involved a number of steps. Firstly, the probability of developing these conditions among inactive people was derived by adjusting the general population age-specific incidence rates using the attributable risk fraction (Jamrozik 2005[57]). Secondly, the estimates were adjusted using RR estimates of the probability of developing the health states among active individuals reported in Hu *et al.*,[50,51,52]

The probability that the primary stroke or CHD event is fatal is based on incidence data from the data from Bromley Coronary Heart Disease Register and the Oxfordshire Community Stroke project Ward *et al.,* 2007[53]). This should be acknowledged as a simplification of the model, as in reality these probabilities might depend on level of physical activity. Lack of data, however, precluded accounting for such a possibility.

Mortality risks

The probability for CVD (CHD and stroke), and non–CVD related mortality for 'healthy people' were derived from age-specific UK interim life tables prepared by the Government Actuary's Department that were adjusted by age-specific UK annual incidence of mortality prepared by the Office of National Statistics (see Appendix 5). Whilst it is recognised that these estimates relate to the general population and hence include people with CHD, stroke and diabetes, the percentage of those disease groups are relatively small (<8%) and hence we assume these estimates are applicable to the 'healthy population.' Relative risk estimates for CHD, stroke and non–CVD related mortality among people with CHD, stroke, and diabetes were used to adjust the probabilities for the 'healthy people' to derive probabilities of CHD, stroke and non-CVD related mortality. The RR estimates for diabetic patients were based on a cohort of Framingham Heart Study (aged 45-74) that were followed for up to 25 years in the Preis *et al.,* study.[58] For stroke patients, data were obtained from Brønnum-Hansen *et al.,* (2001) [59] that followed a Danish cohort of 25 + year olds for 10 years after their first non-fatal stroke. As no equivalent data were found for CHD patients the model assumes CHD risk is the same as stroke risk.

Table 27: Relative risks for mortality after primary events

	After non-fatal CHD	After non-fatal stroke	After diabetes
Non-CVD mortality	1.71	1.71	1.49
CVD mortality	3.89	3.89	2.61

Utility values

Health state utility values were taken from Ward *et al.*,[55] who undertook a wide search for available evidence on utility estimates associated with CVD and diabetes health states (see Table 28).

Table 28: Condition specific utility values Ward *et al.*,[55]

Condition	**Utility**
Healthy	1
CHD initial event	0.8
Post CHD event	0.92
Stroke initial event	0.63
Post stroke event	0.65
Diabetes	0.9

To account for the fact that health-related quality of life (HRQoL) in the general population falls with age, the disease-specific utilities were weighted using age-specific utility scores for the general population. The age specific utility scores were estimated using data from the Health Survey for England (2008), see Table 29.[60]

Table 29: Age-specific quality of life (HSE 2008)

Age	**Mean**	**SD**
33-44	0.90	0.184
45-54	0.86	0.229
55-64	0.82	0.264
65-74	0.78	0.266
75+	0.72	0.275

Process utility

It is acknowledged that individuals benefit psychologically from physical activity, resulting in a so called 'process utility', and it has been estimated that there is an average increase in utility values of 0.072.[10] Using a conservative approach, this utility gain is assumed to last for only the first year as the evidence indicates that this is the period where individuals stayed active in a study by Campbell *et al.*,[61] Sensitivity analysis considers the impact of this QoL gain by setting it to zero in the univariate sensitivity analysis.

Intervention costs

An estimate of the cost of ERS was taken from Pavey *et al.*, and is based on a health technology assessment by Isaacs *et al.*, (2007), which conducted a detailed micro-level costing exercise for a leisure centre based ERS.[10,70] Pavey *et al.*, updated this cost to 2010 prices (£222) and we have inflated this to a 2011/12 cost of £229 using inflation indices from the Personal Social Services Research Unit (2012).[48] The cost to the participants is not included in the ERS model.

Treatment costs

Table 30 shows the annual costs per person attributed to the health states in the model. These costs were taken from a National Clinical Guidelines Centre report that undertook an updated review of costs for various health states.[56]

Individuals incur a one-off initial event cost when entering a CHD or stroke disease state. Furthermore, for all three disease states (CHD, stroke and diabetes) individuals incur an on-going treatment cost for each year they remain in that disease state.

Table 30: Treatment costs related to conditions

Conditions	Annual cost per person (2011/12 prices)
Healthy	£0
CHD initial event	£4,198
CHD annual treatment	£480
Stroke initial event	£10,839
Stroke annual treatment	£2,380
Diabetes annual treatment	£968

Injuries and adverse events

No new data relating to injuries and adverse events were identified in the systematic review and these are therefore not included in this analysis.

Subgroup analysis

Subgroup analysis was carried out for individuals with a diagnosed condition known to benefit from physical activity. The three conditions included in the Pavey *et al.,* HTA were; obesity, hypertension and depression.[10] Table 31 shows the probabilities of being active and inactive associated with these conditions taken from Pavey *et al.,* and the calculated RRs that were used in these sub-group analyses. For events where data were not available, i.e. diabetes for the hypertensive cohort, basecase values have been assumed.

For the depressive subgroup analysis, data from the Murphy *et al.,* study[25] were provided to us (personal correspondence from Professor Murphy, October 8th 2013) which enabled us to estimate the RR of achieving recommended levels of physical activity for ERS in a subgroup of individuals with a mental health referral (1.02, 95%CI 0.83 to 1.24). As these data were more directly applicable to the population with depression we have applied this as the basecase efficacy parameter in this subgroup analysis. For the obese and hypertensive subgroups where no subgroup specific effectiveness data were available we have applied the meta-analysed effectiveness data from all studies included in the clinical effectiveness review, which are not specific to patients with these conditions. The results for the depressive cohort are also provided using these RRs for comparison. All other parameter values are the same as the basecase analysis

Table 31: Data applied in the subgroup analysis[10]

Risks of adverse health outcomes by comorbidity				Calculated RRs
Obese	Probability of experiencing CHD when active	0.0259	CHD	0.6888
	Probability of experiencing CHD when inactive	0.0376		
	Probability of experiencing stroke when active	0.0259	Stroke	0.6888
	Probability of experiencing stroke when inactive	0.0376		
	Probability of experiencing type 2 diabetes when active	0.0756	Diabetes	0.7667
	Probability of experiencing type 2 diabetes when Inactive	0.0986		
Hypertensive	Hypertensive Probability of experiencing CHD when active	0.060	CHD	0.8108
	Probability of experiencing CHD when inactive	0.074		
	Probability of experiencing stroke when active	0.060	Stroke	0.8108
	Probability of experiencing stroke when inactive	0.074		
Depressive	Depressive Probability of experiencing CHD when active	0.0336	Depressive	0.4195
	Probability of experiencing CHD when inactive	0.0801		

Univariate sensitivity analysis

Univariate sensitivity analyses were undertaken to examine the impact of changes to a number of parameter values on the cost-effectiveness results (see, Table 32). Following completion of the report, further additional analyses were requested by the NICE Public Health Appraisal Committee (PHAC). These additional analyses are summarised in Appendices 7 and 8.

Table 32: Overview of univariate sensitivity analysis

Purpose (Impact of)	Parameter	Changes in parameter estimates
Changes in people who become physically active (at 1 year) after exposure to ERS	Effectiveness estimate (via RR)	1) Threshold analysis. At what levels does the ICER fall below £20,000 / £30,000 2) ITT analysis
Changes in persistence of protective effects (adjusted for decay rates) of physical activity.	RR for developing disease conditions	Base case=protective effects persists up to 10 years Changes: 1.Protective effects persist over lifetime =applying the same RR used for the first 10 years for the rest of the lifetime 2. Protective effects persist just for a year = apply RR to first year(rather than 10 years) and the remaining years take RR =1
Changes in discount rate	Discount rate	Change discount rate for costs and QALYs from 1.5% to 3.5%
Assuming no psychological QoL gain from physical activity	Process utility	Change process utility from 0.072 to zero.
Process utility lasts longer	Process utility	Threshold analysis.
Risk of developing disease conditions change.	RR of developing disease	RRs from Pavey *et al.*,[3]}
Lower intervention cost	Intervention cost	Threshold analysis
Change in QoL utility values	QoL utility	QoL utilities from Pavey *et al.*,

Probabilistic analysis

Uncertainties around all parameters in the model (except baseline mortality) are addressed simultaneously using probabilistic sensitivity analyses (PSA). Baseline mortality data were excluded from the probabilistic sensitivity analysis because mortality data come from census data and national databases where the uncertainty in the mean estimates is expected to be small.

The choice of distributions and their respective alpha and beta calculations draws on Briggs *et al.*,[62] In cases, where there are no data on standard errors they were subjectively assigned at 10%

of the mean value. We have checked that the model results are stable and this information was used to determine the number of runs (10,000).

6.1.5 Results

Deterministic results

Table 33 shows the cost-effectiveness results per individual person based on point estimates of parameter values. The deterministic analysis indicates that ERS is expected to produce a small health gain (0.003 QALYs) at an additional cost of £225 as compared against usual care. This resulted in an ICER of £76,059 per QALY gained.

Table 33: Deterministic results

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,572	18.136	£225.4	0.003	£76,059
Usual care	£4,346	18.133			

Probabilistic results

Table 34 shows the PSA results per individual person. The PSA results are very similar to the deterministic results, with an ICER of £76,276.

Table 34: PSA results

	Mean cost (95%CI)	Mean QALY (95%CI)	Incremental cost	Incremental QALY	ICER
ERS	£4,570 (4568, 4571)	18.1284 (18.006, 18.161)	£226	0.0030	£76,276
Usual care	£4,344 (4342, 4346)	18.1254 (18.093, 18.158)			

Figure 18 shows a cost-effectiveness plane of the probabilistic results. Whilst all of the PSA estimates indicate a positive health gain and increase in costs, there is uncertainty in the magnitude of that cost and QALY gain. However, as can be seen from the cost-effectiveness acceptability curve in Figure 19, the probability that ERS is cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained is only 0.004.

Figure 18: Cost-effectiveness plane

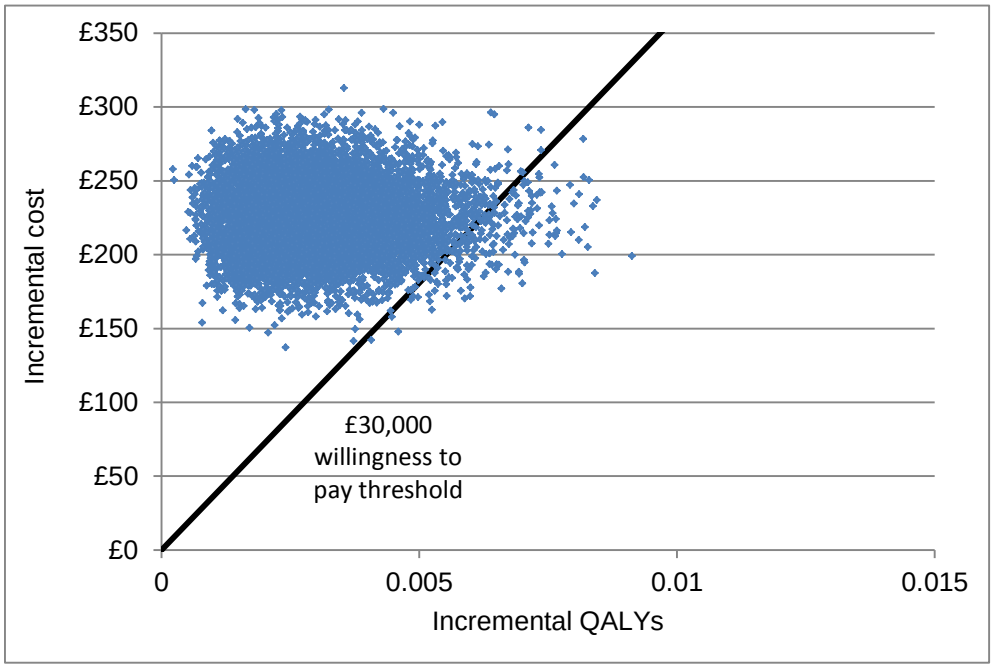
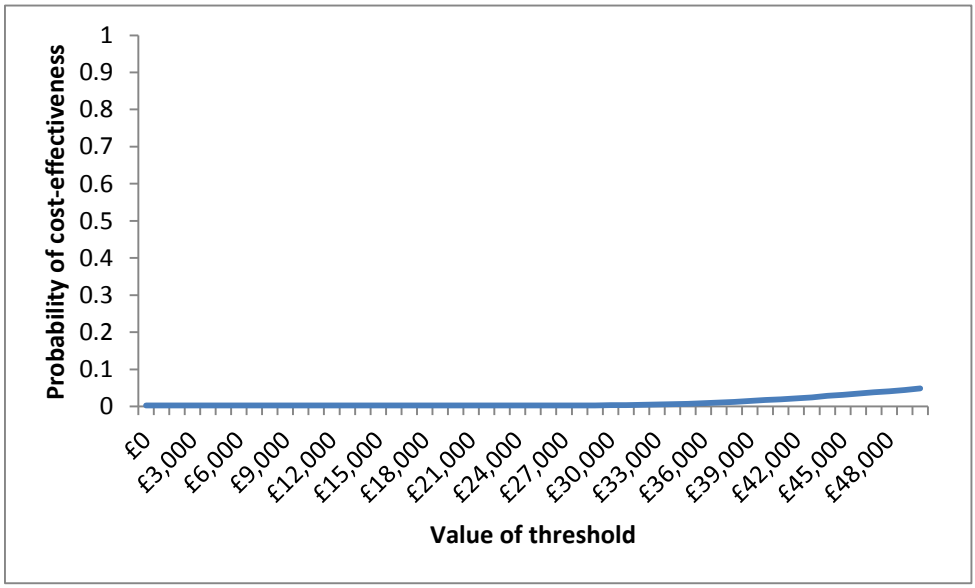


Figure 19: Cost-effectiveness acceptability curve



Univariate sensitivity analysis

Univariate sensitivity analyses were undertaken to examine the impact of assumptions about the effectiveness of ERS, the length of the protective effect of physical activity and the discount rate on the cost-effectiveness of ERS versus usual care. Table 35 lists the effect of these changes.

The model is very sensitive to increases of the RR of ERS on physical activity uptake, with a small increase from 1.12 to 1.31 leading to the ICER falling below £30,000 per QALY gained. Using an ITT approach to estimate the efficacy of ERS compared with usual care reduced the RR to 1.08 and substantially increased the ICER to over £100,000 per QALY. Increasing the protective effect of physical activity over the duration of an individual's lifetime leads to an ICER that is around £33,000 per QALY gained. However, as expected, excluding the process utility raises the ICER considerably, whilst assuming that this utility lasts for four years reduces the ICER to around £28,000 per QALY gained. Using the Pavey *et al.*, RRs of developing physical activity related diseases leads to an ICER of around £38,000. A 60% reduction in the cost of the intervention is required before the ICER falls below £30,000. Using the Pavey *et al.*, utilities results in an ICER of around £62,000.

Table 35: Results of the univariate sensitivity analysis

Parameter	Baseline	Sensitivity analysis	ICER (baseline £76k)
RR of effectiveness of ERS on physical activity uptake	1.12	1.31	<£30,000
		1.47	<£20,000
		1.08 (ITT)	£113,931
Length of protective effect of physical activity	10 years	1 year	£124,193
		lifetime	£33,056
Discount rate	1.5%	3.5%	£88,943
Process utility	0.072	0	£188,834
Process utility threshold analysis: How long does the effect need to last for the ICER to fall below £30,000 per QALY?	First year only	4 years	£27,893
RR of developing disease (active vs. inactive)	CHD 0.9 Stroke 0.86 Diabetes 0.67	0.52 0.73 0.5	£37,676
Intervention cost threshold analysis: reduction required to achieve an ICER <£30,000 per QALY	£229	60% reduction (£92)	£29,746
Utility values for disease states changed to those used by Pavey *et al.*,	CHD initial event 0.8 Ongoing CHD 0.92 Stroke initial event 0.63 Ongoing stroke 0.65 Diabetes 0.90	0.55 0.52 0.70	£62,343

Results for the additional analyses requested by PHAC are summarised in Appendices 7 and 8.

Results of the subgroup analysis

Tables 36, 37, 38 and 39 show the results of the subgroup analysis. In all subgroups the ICER is above £37,000.

Table 36: Obese cohort using basecase RR for effectiveness of ERS

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,764	18.063	£221	0.005	£45,905
Usual care	£4,543	18.058			

Table 37: Hypertensive cohort using basecase RR for effectiveness of ERS

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,632	18.111	£224	0.004	£61,602
Usual care	£4,408	18.107			

Table 38: Depressive cohort using Murphy *et al.*, subgroup data for effectiveness of ERS (personal correspondence from Professor Murphy, October 8th 2013)

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,695	18.035	£228	0.001	£227,948
Usual care	£4,467	18.034			

Table 39: Depressive cohort using basecase RR for effectiveness of ERS

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,688	18.040	£221	0.006	£37,488
Usual care	£4,467	18.034			

6.1.6 Comparison of Anokye adapted to ERS model and Pavey ERS model

The aim of this short report was to adapt the Anokye *et al.*, brief advice model into a model comparing ERS with usual care.[19] The parameters we changed were; replacing the RR of brief advice versus usual care with the same RR of ERS versus usual care used by Pavey *et al.*, changing the starting age from 33 years to 50 years to reflect the Pavey *et al.,* data and inflating all costs to 2011-12 values. The adapted model appears to generate results which are less favourable to ERS even though the effectiveness estimate applied in the updated model is slightly more favourable. We will attempt here to explain why the model results differ in a manner not explained solely by the update of efficacy evidence. We do not have access to the Pavey *et al.*, model and so our explanation of these discrepancies is based on the Pavey *et al.*, health technology report.[3]

Comparison of model structure

The aim of the Pavey model is the same as the adapted model i.e. the impact of ERS on CHD, stroke and diabetes through the beneficial effects of increased physical activity. The intervention (and effectiveness of the intervention), comparator, perspective and time horizons are the same in both models. The two main differences are;

a) Pavey used a decision tree approach whereas the adapted model has a Markov structure;
b) The benefits of physical activity were assumed to be constant over lifetime in Pavey *et al.*, whereas in the adapted model, the benefits of physical activity are limited to 10 years;
c) Many of the input parameters differ as detailed below.

Comparison of input parameters

Relative risks

In Pavey *et al.*, the RR for developing a disease for active versus inactive individuals were 0.52, 0.73 and 0.5 for CHD, stroke and diabetes, respectively. In the adapted model they are 0.9, 0.86 and 0.67, respectively. The effect of using the Pavey *et al.*, RRs is explored in our sensitivity analysis. Table 40 shows the parameters used and describes the sensitivity analysis conducted to explore their impact on cost-effectiveness

Quality of life utility values

Table 40 also shows the health state utility values in the two models. The values used by Pavey *et al.*, are markedly lower than those in the updated model.

Table 40: Parameter inputs to the sensitivity analysis

Change the RRs associated with active vs. inactive people developing a disease to those used by Pavey *et al.*,	RRs:	Current	Pavey *et al.*,
	CHD	0.9	0.52
	Stroke	0.86	0.73
	Diabetes	0.67	0.5
Change the QoL utility values for disease states to those used by Pavey *et al.*,	Health state utility values	Current	Pavey *et al.*,
	CHD initial event	0.80	0.55
	ongoing CHD	0.92	0.55
	Stroke initial event	0.63	0.52
	ongoing stroke	0.65	0.52
	Diabetes	0.90	0.70

Costs

Pavey *et al.*, report the discounted (3.5%) lifetime costs of CHD, stroke and diabetes used in their model, (shown in Table 41 inflated to 2011/12 prices). They also assume an average length of life

years remaining of 18.41, 5.12 and 28.13 for CHD, stroke and diabetes respectively. In order to compare the lifetime costs of Pavey *et al.,* with the updated model we used the following method to estimate lifetime costs in our model:

1. Apply discounting to the estimate of life expectancy for each health condition to estimate the discounted life years gained in each health state.
2. Multiply the discounted life years by the on-going cost of the condition used in the updated model
3. Add on the cost of the initial event for the condition (zero for diabetes) used in the updated model.

Table 41 shows the discounted lifetime costs used in the Pavey *et al.,* model and the estimates from the updated model. The costs vary widely between the two models.

Table 41: Comparison of estimated life-time costs for patients entering a disease health state for the model reported by Pavey *et al.,* and the updated model

Parameter	Pavey model	Updated model
CHD	£18,857	£8,953
Stroke	£2,090	£21,101
Diabetes	£53,512	£10,392

Comparison of results

Table 42 shows the baseline results from Pavey *et al.,* and the deterministic results from the adapted model with the same RR used by Pavey *et al.,* The Pavey *et al.,* model has a smaller incremental cost but gains 2.7 times the number of QALYs, resulting in an ICER around £21,000.

Table 42: Baseline Results from Pavey *et al.*, and the updated model

Updated ERS model	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,572	18.137	£226	0.003	£88,742
Usual care	£4,346	18.134			
Pavey model					
ERS	£2,492	16.743	£169	0.008	£20,876
Usual care	£2,322	16.735			

n.b. Any inconsistencies in the ICERs presented here and those calculated from the presented incremental results are due to decimal rounding

Number of events avoided and QALYs gained

The number of events avoided and the QALYs gained reported by Pavey *et al.*, and from the updated model are shown in Table 43. Exercise referral avoids far more CHD, stroke and diabetes cases in the Pavey *et al.*, model than in the updated model, thus resulting in much a higher incremental QALY gain in the Pavey *et al.*, model. The difference in event rates is related to the differences in the duration of the protective effect of PA and the strength of this protective effect.

Table 43: Comparison of number of events avoided

Event	**Pavey *et al.*,**	**Updated model**
CHD	51	12.6
Stroke	16	6.1
Diabetes	86	9.6
QALYs gained	800	476

6.1.7 Discussion

There are several limitations of the analysis based on the updated model. The model only estimates the impact of physical activity on selected morbidities and the cost-effectiveness of ERS may therefore be underestimated. It is possible that there is a benefit from physical exercise on other morbidities but previous modellers have been unable to find the necessary data.[3] The updated model does not include the impact of adverse events or injuries, however previous authors have commented that they are rare events and are unlikely to affect the results.[3]

A limitation in assessing sub-groups (obesity, hypertension, depression) is that, with the exception of the depression subgroup, the efficacy of ERS is assumed to be the same as the whole inactive population. Further data would be needed on the efficacy of ERS in these subgroups to test this assumption. The model also assumes that the starting utility for these subgroups is the same as the general population. If the starting utility were found to be lower in any of these subgroups, this may have the effect of lowering the incremental QALY gains, resulting in a higher ICER than that generated within our sensitivity analysis.

We were unable to assess whether less intensive exercise referral schemes could be effective at a lower cost and therefore be cost-effective. The sensitivity analysis indicated that schemes would need a 60% reduction in costs to achieve an ICER below £30,000 per QALY gained. However, less intensive schemes may be less effective and so data on effectiveness and costs would be required to assess cost-effectiveness. (This issue is explored in more detail in Appendix 8.)

The very small incremental QALYs gained by ERS mean that the results are very sensitive to small changes in some of the model parameters. A relatively small increase in the efficacy of ERS or a three year increase in the length of the process utility gain both lead to ICERs that are below £30,000 per QALY gained. In contrast, removing the process utility attributed to ERS results in an ICER in excess of £180,000 per QALY gained and using efficacy data from the ITT analysis, which provides a more conservative estimate of effectiveness, (RR, 1.08, 95%CI 1.00 to 1.17) resulted in an ICER of around £114,000.

The ICER estimated by Pavey *et al.*, was much lower than that estimated in the present analysis. However, we found that several parameter changes reduced the ICER, and it was particularly sensitive to changes in the duration over which the process utility was applied. It may be the case that minor changes to a combination of parameter values (i.e. process utility, length of protective effect, RR of developing the disease and the utility values) would bring the ICER down to a value more consistent with that estimated by Pavey *et al.* (This supposition is explored in more detail in Appendices 7 and 8.)

Due to time and data constraints, we were unable to separately model individuals with a pre-existing condition and also those considered to be healthy. The model therefore assumes that patients do not have CHD, stroke or type 2 diabetes at the start of the model. So, whilst the population of interest for the report as a whole includes those with a pre-existing medical

condition, the economic analysis focuses on a cohort without any of these three specific conditions. We have conducted subgroup analyses for individuals who have hypertension, obesity or depression at the start of the model, as these subgroups were already specified within the existing model. However, subgroup specific effectiveness data were only available for the depression subgroup.

The model over simplifies the clinical situation because it does not recognise that more than one of the three conditions can be present in the same individual and also that the presence of one comorbidity may impact the likelihood of experiencing another. Again, we are constrained here to using an existing economic model in which type 2 diabetes, CHD and stroke are treated as mutually exclusive conditions. Also, the model does not account for the fact that stroke patients are at a higher risk of having recurrent strokes and thus the utility loss and additional costs associated with this are not taken into account. The impact of these limitations on the cost-effectiveness of ERS is difficult to estimate.

Given that the effectiveness estimates applied in the model are based on data from 1 year follow-up, good quality data on the sustainability of activity levels would lessen the uncertainty in the model that comes from extrapolating from short to long-term outcomes.

6.1.8 Conclusion

Our analysis indicates that the ICER for ERS compared to usual care is around £76,000 per QALY, although the cost-effectiveness of ERS is subject to considerable uncertainty and is particularly sensitive to the assumptions made regarding the effectiveness of ERS in increasing physical activity and the size and duration of process utility gains.

7. DISCUSSION

7.1 Statement of principle findings

Systematic review of exercise referral schemes

This is an update of an existing reivew[10] and therefore this review uses the search results, data extraction tools, data and findings of that review in this update. One additional RCT[25], additional qualitative data[46] and two additional observational studies[39,40] have been included in this update.

A total of eight RCTs[13,16,19,24,25,30-32] met the inclusion criteria and were included in the review. Six RCTs[13,16,19,25,30,31] compared ERS with usual care which in all cases included some sort of advice regarding physical activity. Two RCTs[19,32] compared an alternative PA-promoting intervention and one RCT[22] compared an alternative form of ERS (i.e. ERS plus SDT intervention) with usual care.

There was considerable heterogeneity in the nature of the exercise/PA intervention across studies. Studies recruited predominantly sedentary middle-aged adults who had evidence of at least one lifestyle risk factor and five of the studies also included individuals with a medical diagnosis (e.g. hypertension, depression). ERS usually took place at a leisure centre and involved 10-12 weeks of exercise intervention and where there was follow-up it took place at 6 and/or 12 months post randomisation. Studies were judged to have a moderate or low overall risk of bias.

The most commonly reported outcome was self-reported PA. When compared with usual care, there was weak evidence of an increase in the number of ERS participants who achieved 90-150 minutes of at least moderate-intensity PA per week at 6-12 months' follow- up (pooled RR 1.12, 95% CI 1.04 to 1.20). There was no difference in PA between ERS versus alternative PA promotion interventions or ERS versus ERS plus SDT at 6–12 months' follow-up. We found no evidence to support differences across subgroups (e.g. age, gender) in terms of the impact of ERS on PA. Murphy *et al.,*[25] found that the intervention was effective in increasing levels of physical activity in those referred for a CHD risk factor. There was no consistent evidence for a difference between ERS and any of the comparator groups in the duration of moderate/vigorous intensity and total PA, physical fitness, blood pressure, serum lipids, glycaemic control, obesity indices

(body weight, BMI, percentage fat), respiratory function, psychological well-being (perception of self-worth, or symptoms of depression or anxiety) or HRQoL.

We found considerable variation across studies in the level of uptake (i.e. attendance at the first induction visit) and adherence to ERS (i.e. completion of the programme) across the 19 included studies (16 observational studies and six RCTs). Uptake levels were higher, on average, in RCTs than in observational studies, although there was no clear difference in adherence between the two. In bivariate and multivariate analyses, women and older people were more likely to take up ERS. In addition, although older people were also more likely to adhere, women were less likely to adhere than men. Very few studies reported associations between ERS uptake or adherence and participant psychosocial factors or programme-level predictors.

A consistent finding in the quantitative studies reporting adherence and uptake is the association between increasing age and likelihood of uptake and adherence to ERS. This reverses the trend seen in the general population, which is a decrease in physical activity with advancing age. A number of factors have been proposed to explain this including; older people are less time-constrained, more likely to value the social interaction offered by the group based approaches and may find it easier to incorporate the scheme exercise activities (such as walking, swimming and cycling) into their everyday life. The only group to show a statistically significant increase in physical activity in the Murphy *et al.*,[25] study were those referred for CHD risk. This group would also have been likely to have been older. Increasing age or CHD risk factors may be confounding factors. It may be these factors work in a complementary manner, with physical activity perceived to be a means of reducing CHD risk and CHD risk a perceived greater threat to those of advancing age.

One issue that may impact on trial results, as suggested in the qualitative review of discussion sections of included trials, is the possibility that those volunteering to participate in the trial in the first place may have been more motivated to become active or increase their physical activity. This may have contributed to the overall finding that physical activity levels increased in both intervention and comparison groups. It is therefore possible that trial participants (and perhaps also ERS participants in general) may be more intrinsically motivated initially to become physically active and thus may differ from the population as a whole in terms of their response to such a programme; according to self-determination theory,[72] intrinsic motivation is more likely to lead to behaviour change that is maintained over the longer term. Therefore, ERSs may be

inadvertently creating inequality in service delivery and failing to reach those most in need of intervention, through the element of self-selection that could creep in in terms of uptake and adherence to the scheme.

In two recent systematic reviews (Orrow *et al.,* 2012 and Campbell *et al.,* 2012), exploring the effectiveness of advice or counselling delivered by health professionals within primary care to promote physical activity; positive benefits were seen with significant increases in self reported physical activity at 12 months. In Campbell *et al.,* (2012) where interventions were limited to 'brief advice' the RR was 1.30 (CI 95%1.12 to 1.50), favouring brief advice over usual care. Neither review found any evidence to support exercise referral schemes over advice or counselling interventions.

This review did find benefit of exercise referral schemes over simply giving advice to promote physical activity. In all of the control groups, advice was given on the value of increasing levels of physical activity. This may have had the effect of reducing the apparent effectiveness of ERS if compared to 'usual care' which might mean no advice to promote levels of physical activity. The quality of 'advice' may not have been as high as that delivered in the brief intervention studies, hence a difference was found between the effectiveness of ERS schemes and advice alone. The presence of bias may also influence the findings in these studies, where only two studies[24,25] attempted to blind at outcome assessment.

7.2 Strengths and limitations of the assessment

7.2.1 Clinical Effectiveness

The strength of this update review is that it was able to use the robust findings of a previous systematic review.[3] The additional data included in this update supported the existing findings.

A rigorous search was carried out to identify any additional RCTs and qualitative studies done alongside the RCTs (sibling studies). The narrow focus of this review in terms of its definition of ERS, meant that similar interventions which may have yielded valuable insights were excluded from the review.

Measuring physical activity by methods of self report has an obvious risk of self report bias. There is no gold standard self-reporting measure of adherence to physical activity or physical activity levels. Many traditional instruments have shortcomings from a clinical perspective.

Physical activity levels are often scored on scales that are not easily converted into a counselling message. It can also be difficult to assess small but clinically significant changes in physical activity levels in a practice situation. Problems with these instruments underscore the challenge of translating research findings into clinical practice. Self report levels of physical activity are the only outcomes that show a significant effect. The reliance on outcomes that are subject to recall bias is a weakness of this review.

7.2.2 Cost-effectiveness

The scope for the economic analysis of ERS for this brief report was to update the Anokye *et al.*, brief advice model[47] with evidence from the updated systematic review on the effectiveness of ERS and to update the costs. As such, we did not conduct a systematic review of the existing evidence on the cost-effectiveness of ERS, which limits our ability to place these results into a broader context. However, we have conducted a detailed comparison with the model used by Pavey *et al.*,[3] to explore why the ICERs differ so much from those previously reported. Several of the assumptions made in our economic evaluation are more conservative than the assumptions made by Pavey *et al.,* In particular, the restriction of benefits to 10 years, which has had a substantial impact on the ICERs, may be considered to be a more reasonable assumption than the lifetime benefits assumed by Pavey *et al.* (This issue is explored in more detail in Appendix 7).

The estimate of process utility gain associated with physical activity, which is a particularly important driver of cost-effectiveness within the model, was based on cross-sectional data.[3] It was included in our basecase analysis as this was the approach taken in the economic evaluation of brief interventions to increase physical activity[47], but was actually excluded from the basecase analysis in the economic evaluation of ERS by Pavey *et al.*,[3] In our clinical effectiveness review, some but not all of the RCTs which reported HRQoL found a statistically significant difference between ERS and usual care, suggesting that this short-term benefit is still relatively uncertain. (This issue is explored in more detail in Appendix 8.)

One of the main limitations of the economic evaluation is that it doesn't fully explore the potential for cost-effectiveness to vary according to the exact nature of ERS or the characteristics of the population to whom it is offered. The cost of an ERS is likely to be highly dependent on the exact nature of that scheme. The incremental cost is also dependent on the provision made to those who received 'usual care' which we assumed to have zero cost. There was substantial variation in both of these factors across the included studies, although our threshold analysis

suggested that large changes in the incremental cost of ERS compared to usual care would be needed to bring the ICER under £30,000. (This issue is explored in more detail in Appendix 8). Whilst we have provided some estimates of the cost-effectiveness of ERS for patients who might be referred for ERS due a pre-existing health condition, this has been achieved by assuming that some data from the general population, such as the relative risks of being physically active, are transferrable to those patients with pre-existing conditions.

Another key limitation of the model is that it only captures the impact of physical activity on three health conditions and it doesn't allow for individuals to have multiple conditions. This fails to capture the many aspects of health that may be influenced by physical activity and the complex relationships that exist between different exercise-related conditions, such as the impact of type 2 diabetes on cardiovascular risk. Also, the model does not account for the fact that stroke patients are at a higher risk of having recurrent strokes and thus the utility loss and additional costs associated with this are not taken into account. The impact of these limitations on the cost-effectiveness of ERS is difficult to estimate.

7.3 Uncertainties

Exercise referral scheme clinical effectiveness

A number of uncertainties remain regarding the clinical effectiveness of ERS

- The potential value of different components of the ERS programme on promoting physical activity
- The long term changes in physical activity behaviour as a result of participating in these schemes
- The extent to which people in the 'advice only' groups changed their levels of physical activity
- Whether the small increases in self-reported PA are clinically significant or lead to clinical significant differences

Exercise referral scheme cost-effectiveness

Good quality data on the sustainability of activity levels, and the magnitude and sustainability of any associated process utility gains, would lessen the uncertainty in the model.

8. CONCLUSIONS

8.1 Implications for service provision

In 2006, NICE commented that there is insufficient evidence for ERS and recommended that the NHS should make ERS available only as part of a controlled trial. Pavey *et al.,* updated the evidence available with the inclusion of four additional trials, and also concluded that there remains very limited support for the potential role of ERS in positively improving levels of physical activity. There was little evidence that interventions incorporated strategies that enabled participants to achieve a sustainable active lifestyle, and very little reference to the development of theoretically based interventions that draw on successful behaviour change techniques. This update supports and reinforces these findings. The additional data from a large, well designed trial, conducted in the UK, which incorporated motivational interviewing, found that ERS improved levels of physical activity, but this was of borderline statistical significance.

8.2 Suggested research priorities

- The findings from both the quantitative and qualitative data, suggest that referral for CHD risk, and increasing age, are stronger predictors both for uptake and adherence to ERS. Interventions targeting older patients, at greater risk of reduced levels of physical activity and with CHD risk may show greater benefit of ERS. This should be further tested in mixed method evaluation, incorporating both RCT evidence and qualitative data, which will enable exploration of the elements of the intervention that are most effective.
- Further research to identify the mediating factors that influence uptake and adherence, with a greater understanding of who benefits and in what circumstances. Fewer men take up exercise referral schemes. Studies that explore the barriers and facilitators that men face in increasing levels of physical activity need to be explored.
- Longitudinal studies that examine the relationship between increased levels of physical activity, and impact on health outcomes.
- Further research needed to explore the effect of interventions with a theoretical basis, and the fidelity of the intervention with that theory.
- Understanding the impact of advice in the control interventions which may have reduced the impact of ERS in studies where ERS is compared with an advice only group.

- Develop trials with a comparator group which addresses a different health behaviour or an intervention for something unrelated (e.g. singing in choirs) that may also have a social benefit to compare with ERS. Consider funding of three arm trials or multiple comparison design trials so that the inpact of 'advice only' can be controlled for.

- Adherence to ERS, as measured by attendance, is only a proxy marker of exercise adherence, particularly as participants are unlikely to adhere to the recommended exercise level by attending one session per week. Further research is required to establish better methods of assessing exercise adherence.

- Expected value of sample information (EVSI) techniques should be used to estimate whether the benefits of conducting further research into the areas identified above, to reduce decision uncertainty and potentially make different recommendations regarding the use of ERS, would outweigh the cost of conducting that additional research. The exiting model could be used as a starting point for that analysis, although it would need to be adapted to ensure that the structural uncertainties identified in this report are reflected within the EVSI in addition to the parameter uncertainty currently included in the PSA.

9. APPENDICES

Appendix 1: Study Protocol

The clinical effectiveness and cost-effectiveness of exercise referral schemes to promote physical activity: A short report.

HTA 13/45/01


Final Protocol.xps

Appendix 2: Literature Search Strategies

Searches were limited by English Language and publication date of October 2009 to current.

Stage One Search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 physical activity referral*.ti,ab.
2 exercise on prescription.ti,ab.
3 exercise referral*.ti,ab.
4 supervised exercise.ti.
5 1 or 2 or 3 or 4
****
Stage Two Search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 "Referral and Consultation"/
2 (exercise* or physical*).ti,ab.
3 1 and 2 (2396)
4 ((physical* or exercise*) adj2 (superv* or subsid* or prescrib*)).ti,ab.
5 (exercise* adj2 (fit* or train* or activit* or promot* or program* or intervention*)).ti,ab.
6 (physical* adj2 (fit* or train* or activit* or promot* or program* or intervention*)).ti,ab.
7 ((physical* or exercise*) and referral*).ti,ab.
8 4 or 5 or 6 or 7
9 Randomized controlled trial.pt.
10 Randomized Controlled Trial/
11 (random$ or placebo$).ti,ab,sh.
12 ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.
13 9 or 10 or 11 or 12
14 controlled clinical trial.pt.
15 (retraction of publication or retracted publication).pt.
16 13 or 14 or 15
17 (family medicine$ or family practice$ or general practice$ or primary care or primary health care or primary health service$ or primary healthcare or primary medical care or family medical practice$ or family doctor$ or family physician$ or family practitioner$ or general medical practitioner$ or general practitioner$ or local doctor$).ti,ab.
18 Family Practice/
19 Primary Health Care/
20 Physicians, Family/
21 Community Health Centers/
22 (community healthcare or community health care).ti,ab.
23 (GP or GPs).ti,ab.
24 general practic*.ti,ab.
25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 (referral* or promot* or program* or intervent*).ti,ab.

27 25 or 26
28 Exercise/
29 Exercise Therapy/
30 28 or 29
31 27 and 30
32 3 or 8 or 31
33 (child* or adolescent* or school* or pediatric* or paediatric*).ti.
34 32 not 33
35 16 and 34
36 (animals not humans).sh.
37 35 not 36
38 ("2009 October*" or "2009 November*" or "2009 December*" or "2010*" or "2011*" or "2012*" or "2013*").dp.
39 37 and 38
40 limit 39 to english language

Appendix 3: Table of excluded studies with rationale

Table 44: Full text exclusion from all systematic review (electronic literature search)

Paper	Comment
Ackermann RT, Deyo RA, LoGerfo JP. Prompting primary providers to increase community exercise referrals for older adults: a randomized trial. *J Am Geriatr Soc* 2005; 53(2):283-289.	Randomisation before baseline assessment
Anokye NK, Trueman P, Green C, Pavey TG, Hillsdon M, Taylor RS *et al.*, The cost-effectiveness of exercise referral schemes. *BMC Public Health* 2011; 11:954.	Cost-effectiveness model
Baker M. Analysis... national guidelines for exercise referral schemes. Practice Nurse 2001; 21(9):14.	Not randomised controlled trial
Beynon CM, Luxton A, Whitaker R, Cable NT, Frith L, Taylor AH *et al.*, Exercise referral for drug users aged 40 and over: results of a pilot study in the UK. *BMJ Open* 2013; 3(5).	Not randomised controlled trial
Bull FC, Milton KE. A process evaluation of a "physical activity pathway" in the primary care setting. *BMC Public Health* 2010; 10.	Not randomised controlled trial
Casey D, De CM, Dasgupta K, Casey D, De Civita M, Dasgupta K. Understanding physical activity facilitators and barriers during and following a supervised exercise programme in Type 2 diabetes: a qualitative study. *Diabet Med* 2010; 27(1):79-84.	Not randomised controlled trial
Chambers MJ. Exercise: a prescription for a good night's sleep? Phys Sportsmed 1991; 19(8):106-112.	Not randomised controlled trial
Cobiac LJ, Vos T, Barendregt JJ. Cost-Effectiveness of Interventions to Promote Physical Activity: A Modelling Study. *PLoS medicine* 2009; 6(7).	Cost-effectiveness model
Corbett C, Woodiwiss B. Exercise on prescription. Professional Nurse 1900; 18(12):666-667.	Not randomised controlled trial
Davies T, Craig A. Developments & opportunities for exercise prescription... This article is the first in a series focussing on issues in exercise prescription. SportEX Medicine 1999;(1):20-22.	Not randomised controlled trial
Dugdill L, Graham RC, McNair F. Exercise referral: the public health panacea for physical activity promotion? A critical perspective of exercise referral schemes; their development and evaluation. Ergonomics 2005; 48(11-14):1390-1410.	Not randomised controlled trial
Elley CR, Garrett S, Rose SB, O'Dea D, Lawton BA, Moyes SA *et al.*, Cost-effectiveness of exercise on prescription with telephone support among women in general practice over 2 years. *BJSM online* 2011; 45(15):1223-1229.	No primary care referral

Elley CR, Kerse N, Arroll B, Robinson E. Effectiveness of counselling patients on physical activity in general practice: cluster randomised controlled trial. *British medical journal* 2003; 326(7393):793-796.	No third-party exercise provider
Gademan MG, Deutekom M, Hosper K, Stronks K, Gademan MGJ, Deutekom M *et al.*, The effect of exercise on prescription on physical activity and wellbeing in a multi-ethnic female population: A controlled trial. BMC Public Health 2012; 12:758.	Not randomised controlled trial
Gidlow C, Johnston LH, Crone D, Morris C, Smith A, Foster C *et al.*, Socio-demographic patterning of referral, uptake and attendance in Physical Activity Referral Schemes. J Public Health (Oxf) /20; 29(2):107-113.	Not randomised controlled trial
Graham RC, Dugdill L, Cable NT. Health practitioner perspectives in exercise referral: implications for the referral process. J Sports Sci 2005; 24(6):636-637.	Not randomised controlled trial
Grandes G, Sanchez A, Sanchez-Pinilla RO, Torcal J, Montoya I, Lizarraga K *et al.*, Effectiveness of physical activity advice and prescription by physicians in routine primary care: a cluster randomized trial. *Arch Intern Med* 2009; 169:694-701.	No primary care referral
Hardcastle S, Taylor A, Bailey M, Castle R. A randomised controlled trial on the effectiveness of a primary health care based counselling intervention on physical activity, diet and CHD risk factors. *Patient education and counseling* 2008; 70(1):31-39.	No primary care referral
Harland J, White M, Drinkwater C, Chinn D, Farr L, Howel D. The Newcastle exercise project: a randomised controlled trial of methods, to promote physical activity in primary care. *British medical journal* 1999; 319(7213):828-832B.	No primary care referral
Hellenius M-L. Prescribing Exercise in Clinical Practice. *Current Cardiovascular Risk Reports* 2011; 5(4):331-339.	Not randomised controlled trial
Jebb SA, Ahern AL, Olson AD, Aston LM, Holzapfel C, Stoll J *et al.*, Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial. Lancet 2011; 378:1485-1492.	No third-party exercise provider
Johnston LH, Warwick J, De Ste CM, Crone D, Sidford A. The nature of all 'inappropriate referrals' made to a countywide physical activity referral scheme: implications for practice. *Health Educ J* /20; 64(1):58-69.	Not randomised controlled trial
Jolly K, Daley A, Adab P, Lewis A, Denley J, Beach J *et al.*, A randomised controlled trial to compare a range of commercial or primary care led weight reduction programmes with a minimal intervention control for weight loss in obesity: the Lighten Up trial.	No third-party exercise provider

BMC Public Health 2010; 10:439.	
Josyula LK. Examination of physical activity for health promotion, and attitudes towards aging, among adults - cross-cultural comparisons; healthcare provider recommendations; toolkit evaluation. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 1942; .71(7-B).	Not randomised controlled trial
Karjalainen JJ, Kiviniemi AM, Hautala AJ, Niva J, Lepojarvi S, Makikallio TH *et al.,* Effects of exercise prescription on daily physical activity and maximal exercise capacity in coronary artery disease patients with and without type 2 diabetes. Clin Physiol Funct Imaging 2012; 32(6):445-454.	No third-party exercise provider
Kolt GS, Schofield GM, Kerse N, Garrett N, Ashton T, Patel A *et al.,* Healthy Steps trial: pedometer-based advice and physical activity for low-active older adults. Annals of family medicine 2012; 10(3):206-212.	Not appropriate population
Kolt GS, Rosenkranz RR, Savage TN, Maeder AJ, Vandelanotte C, Duncan MJ *et al.,* WALK 2.0 - Using Web 2.0 applications to promote health-related physical activity: A randomised controlled trial protocol. *BMC Public Health* 2013; 13:436.	No primary care referral
Lawton BA, Rose SB, Elley CR, Dowell AC, Fenton A, Moyes SA. Exercise on prescription for women aged 40-74 recruited through primary care: two year randomised controlled trial. British medical journal 2008; 337.	No primary care referral
Lawton BA, Rose SB, Raina EC, Dowell AC, Fenton A, Moyes SA *et al.,* Exercise on prescription for women aged 40-74 recruited through primary care: two year randomised controlled trial. *BJSM online* 2009; 43(2):120-123.	No primary care referral
Lawton BA. Exercise on prescription for women aged 40-74 recruited through primary care: two year randomised controlled trial (vol 337, a2509, 2008). *British medical journal* 2009; 339.	No primary care referral
Leung W, Ashton T, Kolt GS, Schofield GM, Garrett N, Kerse N *et al.,* Cost-effectiveness of pedometer-based versus time-based Green Prescriptions: the Healthy Steps Study. Australian journal of primary health 2012; 18(3):204-211.	No primary care referral
Lord JC, Green F. Exercise on prescription: does it work? Health Educ J 1995; 54(4):453-464.	Not randomised controlled trial
Markland D, Tobin VJ. Need support and behavioural regulations for exercise among exercise referral scheme clients: The mediating role of psychological need satisfaction. *Psychol Sport Exerc* 2010; 11(2):91-99.	Not randomised controlled trial

Mckay J, Wright A, Lowry R, Steele K, Ryde G, Mutrie N. Walking on prescription: The utility of a pedometer pack for increasing physical activity in primary care. *Patient education and counseling* 2009; 76(1):71-76.	No primary care referral
Mills H, Crone D, James DV, Johnston LH, Mills H, Crone D *et al.*, Exploring the perceptions of success in an exercise referral scheme: a mixed method investigation. Eval Rev 2012; 36(6):407-429.	Not randomised controlled trial
Murphy MH, McNeilly AM, Murtagh EM. Physical activity prescription for public health. Proceedings of the Nutrition Society 2010; 69(1):178-184.	Not randomised controlled trial
Mutrie N, Doolin O, Fitzsimons CF, Grant PM, Granat M, Grealy M *et al.*, Increasing older adults' walking through primary care: results of a pilot randomized controlled trial. *Fam Pract* 2012; 29(6):633-642.	No primary care referral
Nicolai SPA, Kruidenier LM, Leffers P, Hardeman R, Hidding A, Teijink JAW *et al.*, Supervised exercise versus non-supervised exercise for reducing weight in obese adults. *J Sports Med Phys Fitness* 2009; 49(1):85-90.	No primary care referral
Orrow G, Kinmonth AL, Sanderson S, Sutton S. Republished research: Effectiveness of physical activity promotion based in primary care: Systematic review and meta-analysis of randomised controlled trials. *BJSM online* 2013; 47(1):27.	Not randomised controlled trial
Orrow G, Kinmonth AL, Sanderson S, Sutton S, Orrow G, Kinmonth AL *et al.*, Republished research: effectiveness of physical activity promotion based in primary care: systematic review and meta-analysis of randomised controlled trials.[Reprint of BMJ. 2012;344:e1389; PMID: 22451477]. *BJSM online* 2013; 47(1):27.	Not randomised controlled trial
Phillips EM, Kennedy MA. The Exercise Prescription: A Tool to Improve Physical Activity. *Pm&R* 2012; 4(11):818-825.	Not randomised controlled trial
Pringle A, Gilson N, McKenna J, Cooke C. An evaluation of the Local Exercise Action Pilots and impact on moderate physical activity. Health Educ J 2009; 68(3):179-185.	Not randomised controlled trial
Pugh D, Pugh D. Time to encourage patients to take more exercise. Practitioner 2003; 256(1754):25-28.	Not randomised controlled trial
Richards J, Foster C, Thorogood M, Hillsdon M, Kaur A, Wickramasinghe KK *et al.*, Face-to-face interventions for promoting physical activity. *Cochrane Database Syst Rev* 2013.	Not randomised controlled trial
Rimer J, Dwan K, Lawlor DA, Greig CA, McMurdo M, Morley W *et al.*, Exercise for depression. Cochrane Database Syst Rev 2012;(7).	Not randomised controlled trial
Rouse PC, Ntoumanis N, Duda JL, Jolly K, Williams GC, Rouse PC *et*	Not randomised

al., In the beginning: role of autonomy support on the motivation, mental health and intentions of participants entering an exercise referral scheme. *Psychol Health* 2011; 26(6):729-749.	controlled trial
Rome A, Persson U, Ekdahl C, Gard G. Physical activity on prescription (PAP): costs and consequences of a randomized, controlled trial in primary healthcare (Provisional abstract). Scand J Prim Health Care 2009; 27:216-222.	Part of intervention prior to randomisation
Sabti Z, Handschin M, Joss MK, Allenspach EC, Nuscheler M, Grize L *et al.,* Evaluation of a physical activity promotion program in primary care. *Fam Pract* 2010; 27(3):279-284.	Not randomised controlled trial
Santos C, Santos J, Morais L, Rodrigues F, Barbara C. Pulmonary rehabilitation in COPD: Effects of two aerobic exercise intensity in patient-centered outcomes - A randomized study [Abstract]. Chest 2011; 140:853A.	No primary care referral
Slade SC, Keating JL. Effects of preferred-exercise prescription compared to usual exercise prescription on outcomes for people with non-specific low back pain: a randomized controlled trial [ACTRN12608000524392]. *BMC Musculoskelet Disord* 2009; 10:14.	No primary care referral
Slade SC, Keating JL. Exercise prescription: a case for standardised reporting. BJSM online 2012; 46(16):1110-+.	Not randomised controlled trial
Sorensen J, Sorensen JB, Skovgaard T, Bredahl T, Puggaard L, Sorensen J *et al.*, Exercise on prescription: changes in physical activity and health-related quality of life in five Danish programmes. *Eur J Public Health* 2011; 21(1):56-62.	Not randomised controlled trial
Sukala WR, Page R, Cheema BS, Sukala WR, Page R, Cheema BS. Exercise training in high-risk ethnic populations with type 2 diabetes: a systematic review of clinical trials. [Review]. *Diabetes Res Clin Pract* 2012; 97(2):206-216.	Not randomised controlled trial
Taylor TR, Makambi K, Sween J, Roltsch M, Adams-Campbell LL, Taylor TR *et al.,* The effect of a supervised exercise trial on exercise adherence among African American Men: a pilot study. *J Natl Med Assoc* 2011; 103(6):488-491.	Not randomised controlled trial
Thangaratinam S.Rogozinska. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ (Clinical research ed 2012;). 344(pp e2088):2012.	Not randomised controlled trial
Thangaratinam S.Rogozinska. Interventions to reduce or prevent obesity in pregnant women: A systematic review. Health Technol Assess 2012; 16(31):1-191.	Not randomised controlled trial
Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW *et al.,* Effects of interventions in pregnancy on maternal	Not randomised controlled trial

weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ* 2012; 344:e2088.	
Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Duda W, Borowiack E *et al.*, Interventions to reduce or prevent obesity in pregnant women: a systematic review. [Review]. Health Technol Assess 2001; 16(31):iii-iiv.	Not randomised controlled trial
van MM, Rubinstein SM, Verhagen AP, Ostelo RW, Koes BW, van Tulder MW *et al.*, Exercise therapy for chronic nonspecific low-back pain. [Review] [62 refs]. *Baillieres Best Pract Res Clin Rheumatol* 2010; 24(2):193-204.	Not randomised controlled trial
van Hoecke AS, Delecluse C, Bogaerts A, Boen F. The long-term effectiveness of need-supportive physical activity counseling compared with a standard referral in sedentary older adults. J AGING PHYS ACTIVITY 2013.	No primary care referral
Vermunt PW, Milder IE, Wielaard F, de Vries JH, Baan CA, van Oers JA *et al.*, A lifestyle intervention to reduce Type 2 diabetes risk in Dutch primary care: 2.5-year results of a randomized controlled trial. *Diabet Med* 2012; 29(8):e223-e231.	No primary care referral
Vermunt PW, Milder IE, Wielaard F, de Vries JH, van Oers HA, Westert GP *et al.*, Lifestyle counseling for type 2 diabetes risk reduction in Dutch primary care: results of the APHRODITE study after 0.5 and 1.5 years. *Diabetes Care* 2011; 34(9):1919-1925.	No primary care referral
Voet-Nicoline BM, van der Kooi EL, Riphagen I, I, Lindeman E, van-Engelen-Baziel GM, Geurts-Alexander CH. Strength training and aerobic exercise training for muscle disease. *Cochrane Database Syst Rev* 2013.	Not randomised controlled trial
Voet NB. Strength training and aerobic exercise training for muscle disease. *Cochrane database of systematic reviews (Online)* 2010;(1):CD003907.	Not randomised controlled trial
Voet NB, van der Kooi EL, Riphagen II, Lindeman E, van Engelen BG, Geurts AC *et al.*, Strength training and aerobic exercise training for muscle disease. [Review] [76 refs][Update of Cochrane Database Syst Rev. 2005;(1):CD003907; PMID: 15674918]. *Cochrane Database Syst Rev* 2010;(1):CD003907.	Not randomised controlled trial
Ward M, Phillips CJ, Farr A. Heartlinks -- a real world approach to effective exercise referral. International Journal of Health Promotion & Education 2010; 48(1):20-27.	Not randomised controlled trial
Waryasz GR, McDermott AY. Exercise prescription and the patient with type 2 diabetes: A clinical approach to optimizing patient outcomes. *J Am Acad Nurse Pract* 2010; 22(4):217-227.	Not randomised controlled trial

Wu YT, Hwang CL, Chen CN, Chuang LM, Wu YT, Hwang CL *et al.,* Home-based exercise for middle-aged Chinese at diabetic risk: a randomized controlled trial. *Preventive medicine* 2011; 52(5):337-343.	No primary care referral
Wyatt-Williams J. Setting Up A National Exercise Referral Scheme (in Wales). Journal of aging and physical activity 2012; 20:S259.	Not randomised controlled trial
Yildirim Y, Soyunov S, Yildirim Y, Soyunov S. Relationship between learning strategies of patients and proper perception of the home exercise program with non-specific low back pain. J Back Musculoskeletal Rehabil 2010; 23(3):137-142.	No primary care referral
Yoshida H, Ishikawa T, Suto M, Kurosawa H, Hirowatari Y, Ito K *et al.,* Effects of Supervised Aerobic Exercise Training on Serum Adiponectin and Parameters of Lipid and Glucose Metabolism in Subjects with Moderate Dyslipidemia. Journal of atherosclerosis and thrombosis 2010; 17(11):1160-1166.	Not randomised controlled trial
Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S, Zanuso S *et al.,* Exercise for the management of type 2 diabetes: a review of the evidence. [Review] [37 refs]. *Acta Diabetol* 2010; 47(1):15-22	Not randomised controlled trial
Zhang XD, Long BB, Wu H. Effects of Aerobic Exercise Prescription Intervention to Female College Students with Simple Obesity. Proceedings of the 21St Pan-Asian Congress of Sports and Physical Education, Vol 4: Application of Physiology and Psychology in Sports 2010;87-89.	No primary care referral
Zuazagoitia A, Grandes G, Torcal J, Lekuona I, Echevarria P, Gomez MA *et al.,* Rationale and design of a randomised controlled trial evaluating the effectiveness of an exercise program to improve the quality of life of patients with heart failure in primary care: The EFICAR study protocol. BMC Public Health 2010; 10:33.	No third-party exercise provider

Appendix 4: Inputs for PSA

Parameter	mean	standard error	distribution
Incidence rates for:			
CHD (available by age groups)			
33-34	0.000035	1.0881E-05	beta
35-44	0.000465	3.9654E-05	
45-54	0.002095	8.41E-05	
55-64	0.00631	0.00014565	
65-74	0.0097	0.00018027	
75-81	0.0097	0.00018027	
Stroke (available by age groups)			
33-34	0.00008	2.7602E-05	beta
35-44	0.00023	4.6797E-05	
45-54	0.00057	7.3658E-05	
55-64	0.00291	0.00016623	
65-74	0.0069	0.00025546	
75-81	0.01434	0.0003669	
Diabetes (available by age groups)			
33-39	9.00365E-05	6.9895E-06	beta
40-49	0.000280353	1.2332E-05	
50-59	0.000631793	1.851E-05	
60-69	0.001004529	2.3336E-05	
70-79	0.001115584	2.459E-05	
80-81	0.001115584	2.459E-05	
Probability:			
Fatality cases for CHD			
33-34	0.08773	0.008773	beta
35-44	0.08773	0.008773	
45-54	0.08773	0.008773	
55-64	0.11553	0.011553	
65-74	0.21065	0.021065	
75-81	0.14763	0.014763	
Fatality cases for stroke			
33-34	0.234636872	0.02346369	beta
35-44	0.234636872	0.02346369	
45-54	0.234636872	0.02346369	
55-64	0.23279352	0.02327935	
65-74	0.23466258	0.02346626	
75-81	0.23420074	0.02342007	

Parameter	mean	standard error	distribution
Relative risks for:			
To be active (at year 1) as a result of exercise referral	1.1	0.06	lognormal
Developing disease conditions for active people:			
CHD	0.90	0.04	lognormal
Stroke	0.86	0.04	
T2 Diabetes	0.67	0.12	
Non-CVD mortality after:			
non-fatal CHD	1.71	0.14	lognormal
non-fatal Stroke	1.71	0.14	
diabetes	1.49	0.13	
CVD mortality after:			
non-fatal CHD	3.89	0.04	lognormal
non-fatal Stroke	3.89	0.04	
diabetes	2.61	0.14	
Utility			
Age specific quality of life			
45-54	0.86	0.01	beta
55-64	0.82	0.01	
65-74	0.78	0.01	
75+	0.72	0.01	
Health state utility weight			
Healthy	1.00	0.10	gamma
CHD 1st event	0.80	0.08	
Ongoing CHD	0.92	0.09	
Stroke initial event	0.63	0.06	
Ongoing stroke	0.65	0.07	
Diabetes	0.90	0.09	
Mental health gain	0.07	0.04	beta
Cost			
Exercise referral	£229	£23	normal
CHD 1st event	£4,198	£395	
Ongoing CHD	£480	£45	
Stroke initial event	£10,839	£1,019	
Ongoing stroke	£2,380	£224	
Diabetes	£968	£91	

Appendix 5: Mortality data

Age	All cause mortality	CVD cause mortality	Non -CVD cause mortality
50	0.002854	0.00054	0.00231
51	0.003087	0.00059	0.00250
52	0.003413	0.00065	0.00276
53	0.003693	0.00070	0.00299
54	0.004115	0.00078	0.00333
55	0.004513	0.00086	0.00366
56	0.004949	0.00094	0.00401
57	0.005334	0.00101	0.00432
58	0.005799	0.00110	0.00470
59	0.006403	0.00122	0.00519
60	0.006948	0.00132	0.00563
61	0.007478	0.00142	0.00606
62	0.008051	0.00153	0.00652
63	0.009034	0.00172	0.00732
64	0.010004	0.00190	0.00810
65	0.010801	0.00240	0.00840
66	0.011984	0.00266	0.00932
67	0.013043	0.00290	0.01015
68	0.014685	0.00326	0.01142
69	0.016104	0.00358	0.01253
70	0.017616	0.00391	0.01370
71	0.01932	0.00429	0.01503
72	0.021385	0.00475	0.01663
73	0.023881	0.00531	0.01858
74	0.026280	0.005838	0.020442
75	0.029173	0.007763	0.021410
76	0.032836	0.008737	0.024098
77	0.036376	0.009679	0.026696
78	0.040763	0.010847	0.029916
79	0.045782	0.012183	0.033600
80	0.051718	0.013762	0.037956
81	0.057861	0.015397	0.042465
82	0.064138	0.017067	0.047071
83	0.071322	0.018979	0.052343
84	0.080421	0.021400	0.059021
85	0.089901	0.023922	0.065978
86	0.099902	0.026584	0.073318
87	0.110316	0.029355	0.080961
88	0.122565	0.032614	0.089951
89	0.128800	0.034274	0.094527
90	0.143003	0.038053	0.104951
91	0.153263	0.040783	0.112480
92	0.175290	0.046644	0.128646
93	0.194175	0.051670	0.142505

94	0.214034	0.056954	0.157080
95	0.233037	0.062011	0.171026
96	0.251844	0.067015	0.184829
97	0.269651	0.071754	0.197898
98	0.290335	0.077258	0.213078

Age	**All cause mortality**	**CVD cause mortality**	**Non -CVD cause mortality**
74	0.02628	0.00584	0.02044
75	0.029173	0.00776	0.02141
76	0.032836	0.00874	0.02410
77	0.036376	0.00968	0.02670
78	0.040763	0.01085	0.02992
79	0.045782	0.01218	0.03360
80	0.051718	0.01376	0.03796
81	0.057861	0.01540	0.04246

Sources: ONS, GAD

Appendix 6: Data Extraction

Data Extraction Sheet for ERS update

Part 1: Background information of study

Study ID	177
Reviewer ID	FC
Date of completion of this form	13-7-13
Title of report	An Evaluation of the effectiveness and cost effectiveness of the National ERS in Wales UK: a RCT of a public health policy initiative
Source (journal, year, volume, pages)	J Epidemiol Community Health 21012; 66: 745 to 753
Authors	Murphy *et al.,*
Language of publication	English
Type of report (e.g. full paper/abstract/ unpublished)	Full paper

Part 2: Information about the study

Characteristics of the trial	
Country of the principal investigators, where the trial was conducted	UK
Funders of the trial	
Date trial was conducted	
Type of trial design (e.g. parallel or cluster trial)	
Was the trial multicentre? If so, how many centres were there?	
Follow-up	

Characteristics of the referral	
Who made the referral	Clinician
Reason for referral	Identified opportunitistically by clinicans in normal practice and were provided with basic trial inoformation
Format of referral	form
Referred to who	Evaluation team
Referred to where	Delivered at leisure cenres by exercise professionals in each local health board. Consultations were based on motivation interview principles witch facilitatied patient – centred achievable goals, included relapse prevention strategies at 4 and 16 weeks to review goals and encourage attendance. The
Single or group sessions	
Referral quote from paper	

Characteristics of the intervention	
Components of the intervention	16 week tailored programme of exercise supervised by a qualified exercise professional. Initial consultation with exercise professional on entry: lifestyle questionnaire, health check, introduction to leisure centre facilitates, motivation interview and goal setting. Access to one to one exercise instruction and/or group exercise classes. Discounted rate for exercise act ivies, £1 per session. Four week telephone contact with exercise professional , review of goals, motivation interview, relapse prevention. Sixteen week consultation with exercise professional – review of goasl, motivational interview, health check, lifestyle questionnaire, service evaluation questionnaire and advice on continuing with exercise after the programme. 8 months telephone contact by exercise professional to ask about their exercise behaviour and relapse prevention. 12 months review including repeat of health check carried out at entry and Chester fitness step test.
Total duration	16 weeks
No. of sessions per week	See above
Duration of sessions	See above
Session intensity	See above
Session mode	See above
Control group	Usual care and a leaflet highlighting the benefits of exercise, and were given the addresses of local facilities.
Other information	Motivational interviewing ?fidelity

Characteristics of participants		
	Experimental group	**Control group**
Inclusion criteria	Sedentary and had at least one medical condition. Sedentaqry (identigid as not moderately active for > 3 tiems per week or deconditioned through age or inactivieyt) and have at least one of the following medical conditions: CVD risk factors: Raised BP more that 140/90 ut < 180/100. - Weight managemt - BMI >28 - Controlled diabetes - Imparired glucose tolerance - Hight cholesterol> 5.0 - Family history of heart disease or diabetes - Referral from Cardiac Rehabilitation Schemes Mental Health -mild anxiety, depression or stress Musculoskeletal -at risk of osteioporoisi -arthritis (mild) -poor mobility -musculosketal pain includeing back pain Respiratory/pulmonary -COPD Mild/moderate well controlled (asthma, bronchitis, emphysema) Neurological conditions -Multiple sclerosis Other -Smoker - Chronic fatigure	
Exclusion criteria	Aged < 16 years - Unstable angina - - Blood pressure 180/100 (in either) or above and/ or uncontrolled or poorly controlled hypertension - Cardiomyopathy - Uncontorlled tachycardia - Cardian arrhythmias - Valvular heart disease Diagbetes Uncontgrolled eor poortly	

	controlled epilepsy Congentiatl heart disease - Unexplained dizzy spells - Excessive or unexplained b reathlessness or exertion - Uncontrolled or poorly controlled si	
Total number of randomised participants	1080	1080
Information on the age of the participants (mean and SD)	52 (14.7)	
Information on the sex of the participants (%)	66% women	
Information on the ethnicity of the participants (%)	96% white	
Specifics of the population (i.e. disease %)	CHD risk factors (72%) CHD and mentoal health issues (24%)	

Type of outcomes (What outcomes were assessed in this trial? Which of these outcomes have reported information about the result?)	
Outcome (domain)	**Assessed (measure)**
Effectiveness	
PA	7 day physical activity recall administered by telephone with interviewees blind to group allocation.
Fitness (e.g.VO_{2max})	
Clinical factors (e.g. blood lipids)	
Psychological well-being	HADS anxiety score and HADS depression score
QoL	EQ-5D
Patient satisfaction	
Adverse events	
Patient factors	
Uptake	
Adherence	

Part 3: Extracted results

	ERS (baseline)			**Usual care (baseline)**		
	Mean	**n**	**SD**	**Mean**	**n**	**SD**
PA						
BMI						
Depression: Geriatric						
Depression Scale						
Anxiety: State Trait Anxiety Inventory						
Anxiety/depression EQ-5D						
	ERS (6 months)			**Usual care (6 months)**		
	Mean	**n**	**SD**	**Mean**	**n**	**SD**
BMI						
Depression: Geriatric						
Depression Scale						
Anxiety: State Trait Anxiety Inventory						
Anxiety/depression EQ-5D						
	ERS (12 months)			**Usual care (12 months)**		
	Mean	**n**	**SD**	**Mean**	**n**	**SD**
PA	200 (median)	IQR 60,435		165 (median)	IQR 50,370	
BMI						
Depression: Geriatric						
Depression Scale	HADS 6.14	471	5.73 to 6.54	HADS 6.93	506	6.53 to 7.32
Anxiety/depression EQ-5D	HADS 7.82	472	95% CI 7.39 to 8.25	8.35	502	95% CI 7.92 to 8.77

Part 4: Study Quality

Quality	Yes	Unclear	No
Power calculation reported	Sample size was determined to detect a difference in toal minutes of weekly activiey at 12 monhths, with 1052 participants in each group providing 90% power to detect an effect size of 0.15 with no loss to follow-up and more realistically 87% and 84% power to detect an effect size of 0.15 if 20% and 25% repectively or randomised participants who were lost to follow-up.		
Method of random sequence generation described?	Randomly assigned to the intervention or controla using a random number generatore, with gender and LHB as stratificatiohn variables.		
Method of allocation concealment described?	yes		
Method of outcome (assessment) blinding described?	yes		
Are groups similar at baseline?	yes		
Was ITT analysis used?	yes		
Was there any statistical handling of missing data?	yes		
Were missing data (dropout and loss to follow-up) reported?	yes		
Do you have any additional comments to make about this study?			
Does the reference list of this paper contain additional studies that should be considered for inclusion?			
Is further information required from the authors? If so, give details mean and sd requested.			

APPENDIX 7: Additional analyses conducted prior to the first committee meeting

A7.1 Introduction

Prior to the first Committee meeting we were asked to by the Centre for Public Health Practice to provide some additional analyses to inform the Committee's discussions. In particular we were asked to provide additional analyses to support the following statement in section 6.1.7, "It may be the case that minor changes to a combination of parameter values [……..] would bring the ICER down to a value more consistent with that estimated by Pavey *et al*[10]."

Based on the univariate sensitivity analyses already conducted, it can be seen that the model is sensitive to the duration of protective effect associated with physical activity for the conditions CHD, stroke and diabetes. In the basecase analysis, the duration of protective effect was limited to 10 years. However, the RR estimates applied in the model were based on cohort studies with follow up periods of 19 years for CHD[50] and stroke[51] and 12 years for diabetes.[52] We have therefore decided to explore the possibility of extending the protective effect to reflect the durations of these studies.

The model is also particularly sensitive to the process utility gain attributable to becoming physically active. In the basecase analysis it is assumed that the process utility gain associated with physical activity is applied for one year only, as this is the duration of follow-up for the effectiveness studies. Without studies providing longer-term follow-up it is unclear how long people remain physically active. However, it is likely that some people who continue to be physically active at one year will carry on being physically active in the longer-term. To explore the impact of a gradual fall-off in the number remaining physically active, we have applied the process utility for 10 years, but assumed a linear decrease in the number who are physically active over those 10 years, such that none are receiving a process utility gain from being physically active after 10 years.

We also explored the effect on the ICER of combining these two less conservative assumptions regarding the longer-term benefits of ERS.

A7.2 Results

Presented below are deterministic results for the whole cohort eligible to receive ERS for several scenarios exploring less conservative model assumptions.

Extending the duration of the protective effect associated with physical activity to 19 years for CHD and stroke and 12 years for diabetes, to reflect the follow-up periods in the studies used to estimate the RRs applied in the model, reduced the ICER to £50,634 as seen in Table A7.8.

Table A7.8: Duration of protective effect extended to 19 years for CHD and stroke and 12 years for diabetes

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,527	18.152	£221	0.004	£50,634
Usual care	£4,306	18.148			

Applying the process utility for 10 years, but assuming a linear decrease in the number who are physically active over those 10 years gave an ICER of £21,918, when all other assumptions were held constant, as shown in Table A7.9.

Table A7.9: Number remaining physically active falls linearly to zero over 10 years

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,572	18.218	£225	0.010	£21,918
Usual care	£4,346	18.208			

Results when combining the extended duration of protective effect, with the gradual fall-off in the proportion remaining active are presented in Table A7.10, which shows an ICER of £18,935.

Table A7.10: Duration of protective effect extended and number remaining physically active falls linearly to zero over 10 years

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,527	18.234	£221	0.012	£18,935
Usual care	£4,306	18.222			

The additional analyses conducted, which explore the effect on the ICER of applying some less conservative model assumptions, demonstrate that ICERs as low as £19,000 per QALY can be achieved by combining a gradual fall-off in physical activity over 10 years and extending the

duration of protective effect beyond 10 years. This supports the statement made in section 6.1.7 that "It may be the case that minor changes to a combination of parameter values [……..] would bring the ICER down to a value more consistent with that estimated by Pavey *et al.*[10]"

APPENDIX 8 Additional analyses conducted prior to the second committee meeting

A8.1 Introduction

Following the first Public Health Appraisal Committee (PHAC) on Exercise Referral Schemes, NICE requested that ScHARR-TAG conduct additional analyses to inform the Committee's discussion at the second PHAC. Incremental cost-effectiveness ratios were requested for a 'combined scenario analysis' incorporating;

- Costs for providing brief advice in the comparator arm
- Efficacy estimates from the intention to treat analysis
- A 10-year linear fall-off in the process utility associated with being physical active, applied in combination with the original basecase assumption that the protective effects of exercise are limited to 10 years

It should be noted that the assumptions incorporated into this 'combined scenario analysis' requested by NICE do not necessarily reflect the authors' preferred model assumptions.

In addition, several sensitivity analyses were also requested in which individual changes were made to the combined scenario analysis. Firstly a sensitivity analysis was requested exploring the impact of using EQ-5D data from the Murphy *et al.*[29] study as an alternative to the process utility gain estimated by Pavey *et al.*[10] and applied in the model used to inform the PH44.[63] Secondly, a sensitivity analysis was requested exploring the cost-effectiveness of less intensive ERS. Finally a threshold analysis was also requested on the intervention cost for ERS.

Further details on the methods used to conduct these analyses are provided in section A8.2, and the results are presented in section A8.3.

A8.2 Methods

A8.2.1 Incorporating costs for brief advice

In the main report it was noted that in all of the studies comparing exercise referral to usual care, patients randomised to the usual care arm received some form of advice regarding physical activity. In the model used by Pavey *et al.*[10], no cost was attributed to providing usual care in the comparator arm, which may have overestimated the incremental cost of ERS relative to usual care. In the appraisal of brief advice to promote physical activity, the cost of brief advice was estimated at £9.50 (2010/11 prices).[63] This was inflated to a 2011/12 cost of £9.81 using inflation indices from the Personal Social Services Research Unit (2012)[64] and applied in the combined scenario analysis presented below.

A8.2.2 Intention to treat analysis

In the main report efficacy results were meta-analysed using two different approaches. In Figure 2 the denominators used to calculate the relative risks (RRs) were the number of patients with data at follow-up for each study, whilst in Figure 3, in order to assess the potential (attrition) bias in using completers, the denominators of these three studies were adjusted to all individuals randomised in order to perform an ITT analysis. The cost-effectiveness results presented in the main report used the efficacy data based on individuals with follow-up (RR 1.12, 95%CI 1.04 to 1.20). In the combined scenario analysis presented below we use the efficacy data based on the ITT analysis (RR, 1.08, 95%CI 1.00 to 1.17).

A8.2.3 Duration of protective effect and process utility gain

In the model used to inform PH44[63], the protective effect of physical activity on stroke, type 2 diabetes and CHD was assumed to last for 10 years and a process utility associated with being physically active was assumed to apply for 1 year. In Appendix 7 we presented analyses exploring the impact of increasing the assumed duration of protective effect and the assumed duration over which the process utility is applied. In the combined scenario analysis presented below, we assume that the duration of protective effect is maintained at 10 years, but that there is a linear fall-off in the process utility gain over this 10 year period. This would be consistent with assuming that the number continuing to be physically active falls linearly over the 10 years after the intervention, and that the full process utility gain is experienced until the individual stops being physically active.

A8.2.4 Process utility gain

The process utility gain associated with being physically active reported by Pavey *et al.*[10], and applied in the economic model used to inform PH44[63], is based on cross-sectional data and therefore may not represent a causal relationship between physical activity and health utility. However, Murphy *et al.*[29] report EQ-5D utility scores at 12 months for patients randomised to ERS and usual care allowing the utility gain attributable to ERS to be calculated directly from a randomised comparison. Table 16 of the main report presents the mean EQ-5D scores from the two trial arms as 0.64 (sd 0.32, n=395) and 0.61 (sd 0.32, n=391) for ERS and usual care respectively, giving a mean difference of 0.03 (SE=0.023). It should be noted that this cannot be compared directly against the process utility of 0.072 given by Pavey *et al*., as the value from Pavey et *al.* is an estimate of the difference between those who are physically active and those who are not physically active, whilst the value from Murphy *et al.* is the difference between the randomised groups, each of which had a different proportion who became physically active.

In the additional sensitivity analysis reported below, we have removed the process utility gain of 0.072 which was applied in the basecase analysis to all those who were physically active at 1 year and added 0.03 to the utility values for all those receiving ERS. Nothing is added to the utility values of those receiving usual care as this gain is measured relative to usual care. In this sensitivity analysis it is assumed that the utility gain measured by Murphy *et al.*[29] is experienced for only one year as this is the duration of study follow-up. Whilst it may be assumed that the process utility gain of being physically active may extend beyond the study duration, if people remain physically active, the utility gain associated with receiving ERS is the average gain across those who become active and those who do not and therefore it cannot be extrapolated in the same manner as there is no rationale for a continued utility gain in those who received ERS but did not become physically active.

A8.2.5 Less intensive ERS

In this sensitivity analysis we considered how the cost-effectiveness of a less intensive form of ERS might differ from that assumed in the basecase using evidence on a walking-based intervention (as opposed to a structured leisure centre-based intervention) from Isaacs *et al*.[17] This replicates a similar sensitivity analysis conducted by Pavey *et al.*[10] in which they reduced their intervention costs from £222 to £110. In our sensitivity analysis, the cost of the walking-based intervention was inflated to a cost of £114 (2011/12)[64] to reflect current prices. We assumed that there was no change in efficacy associated with moving to a less intensive ERS.

A8.2.6 Threshold analysis on the intervention cost for ERS

A threshold analysis was conducted in which the intervention cost for ERS was lowered until the ICER reached the £20,000 and £30,000 per QALY threshold boundaries, whilst holding constant all other data and assumptions applied in the combined scenario analysis.

A8.3 Results

A8.3.1 Main results for the cohort eligible to receive ERS

The individual and combined effects of each of the changes to the model assumptions described in section 2 are presented in Table A8.1. It can be seen that the addition of costs for providing some brief advice related to physical activity in the usual care arm has little effect on the ICER. The application of the ITT efficacy data does have a small effect on the incremental costs but a greater proportionate effect on the incremental QALYs, resulting in a substantial increase in the ICER. Allowing for a 10 year linear reduction in the proportion remaining active, and therefore accruing a process utility gain, results in a substantial increase in incremental QALYs from 0.003 to 0.010 and results in the ICER falling to £21,918. The combined effect of all of three changes to the previous basecase gives an ICER of £31,081 for the combined scenario analysis.

Table A8.1: Individual and combined effects of revised model assumptions

Scenario	Description	ERS		Usual care		Incremental		ICER
		Cost	QALYs	Cost	QALYs	Cost	QALYs	
NA	Previous basecase	£4,572	18.136	£4,346	18.133	£225	0.003	£76,059
1	Added cost of brief advice in the usual care arm	£4,562	18.136	£4,346	18.133	£216	0.003	£72,748
2	ITT RR	£4,573	18.135	£4,346	18.133	£227	0.002	£113,931
3	10 year fall-off in process utility	£4,572	18.218	£4,346	18.208	£225	0.010	£21,918
1+2+3	**Combined scenario analysis**	**£4,563**	**18.216**	**£4,346**	**18.209**	**£217**	**0.007**	**£31,081**

Table A8.2 shows the probabilistic sensitivity analysis results per individual person for the combined scenario analysis estimated from 10,000 samples. The PSA results are very similar to the deterministic results, with an ICER of £31,009

Table A8.2: PSA results for the combined scenario analysis

	Mean cost (95%CI)	Mean QALY (95%CI)	Incremental cost	Incremental QALY	ICER
ERS	£4,559	18.2154	£217	0.0070	£31,009
Usual care	£4,343	18.2084			

Figure A8.1 shows a cost-effectiveness plane of the probabilistic results for the first 1000 samples. The cost-effectiveness acceptability curve in Figure A8.2 shows the probability that ERS is cost-effective at various willingness-to-pay thresholds (estimated from the full 10,000 samples). The probability that ERS is cost-effective compared to usual care is 0.41 for a willingness to pay threshold of £30,000 per QALY gained and 0.15 for a willingness to pay threshold of £20,000 per QALY

Figure A8.1: Cost-effectiveness plane for the combined scenario analysis

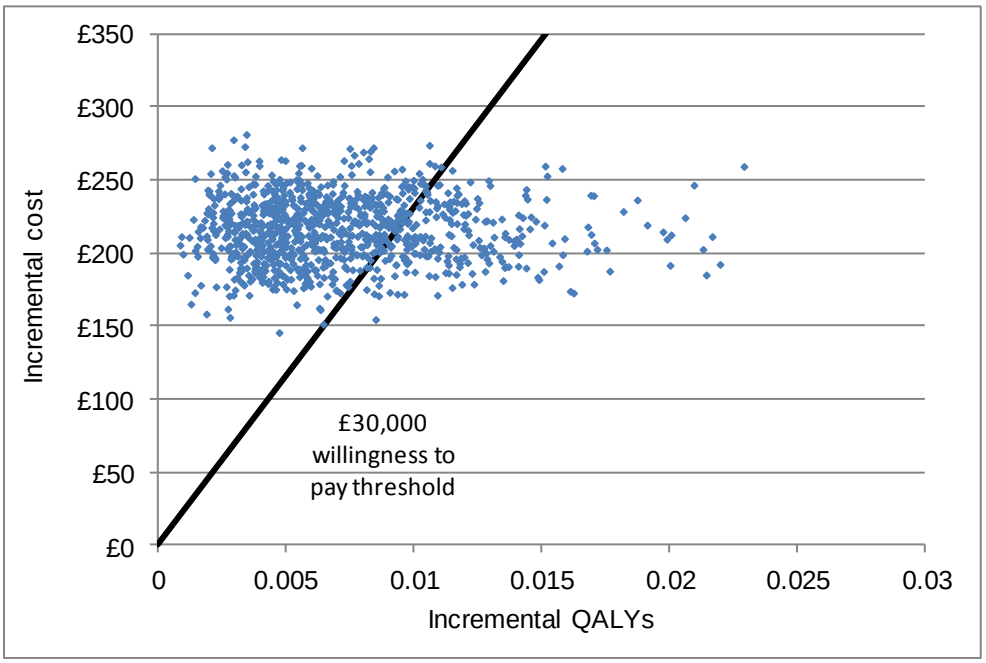
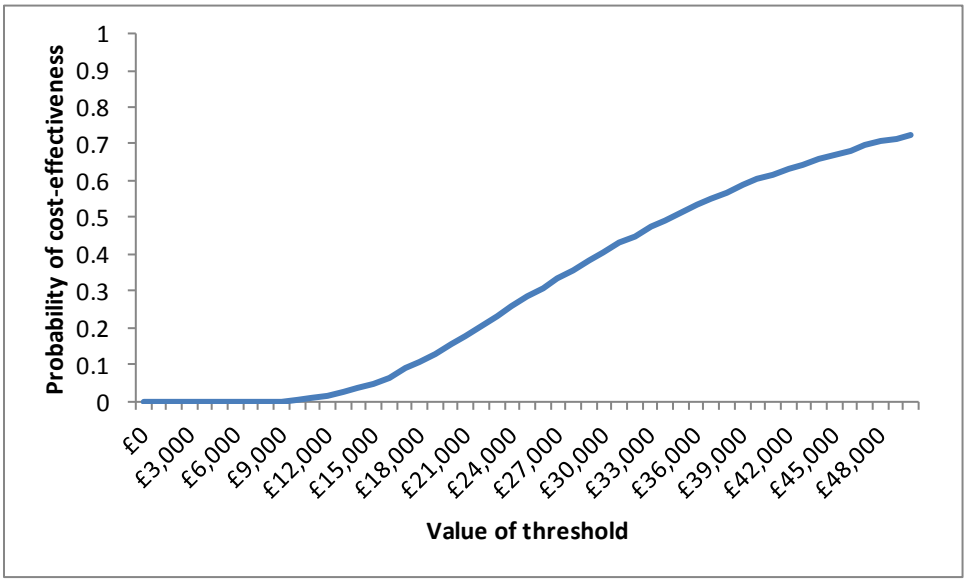


Figure A8.2: Cost-effectiveness acceptability curve for the combined scenario analysis



A8.3.2 Subgroup analysis

The results for the subgroup analysis using the combined scenario analysis assumptions are presented in Tables A8.3 to A8.6 below. When assuming that the effectiveness of ERS in each of these subgroups is similar to that in the eligible population as a whole, the ICERs are marginally more favourable than for the whole population due to the greater risks of conditions associated with inactivity in these subgroups. However, applying the subgroup data for the depressed cohort from the Murphy *et al.* study resulted in a much higher ICER which reflects the estimate of low efficacy for this subgroup within the study reported by Murphy *et al.*[29]

Table A8.3: Obese cohort using basecase RR for effectiveness of ERS

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,757	18.142	£213.8	0.008	£26,015
Usual care	£4,543	18.134			

Table A8.4: Hypertensive cohort using basecase RR for effectiveness of ERS

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,624	18.191	£215.8	0.007	£29,056
Usual care	£4,408	18.183			

Table A8.5: Depressive cohort using Murphy *et al.* subgroup data for effectiveness of ERS (personal correspondence from Professor Murphy, October 8th 2013)

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,685	18.112	£218.0	0.002	£96,462
Usual care	£4,467	18.110			

Table A8.6: Depressive cohort using basecase RR for effectiveness of ERS

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,681	18.119	£213.8	0.009	£23,903
Usual care	£4,467	18.110			

A8.3.3 Additional sensitivity analyses

The sensitivity analysis in which the process utility gain for ERS versus usual care has been estimated directly from the Murphy *et al.* study[29] is reported in Table A8.7. The QALY gain is similar to that reported by Murphy *et al.* (0.03) as it is largely driven by the utility gains derived during the 1 year trial period. Compared to the combined scenario analysis which uses the process utility gain attributable to being physically active, the QALY gain attributable to ERS is over three times greater (0.026 versus 0.007) when estimated using this directly measured EQ-5D resulting in an ICER of £8,290.

Table A8.7: Sensitivity analysis applying the process utility gain estimated from Murphy *et al.* but limiting its application to 1 year

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,563	18.142	£217	0.026	£8,290
Usual care	£4,346	18.115			

The sensitivity analysis applying costs from a less intensive intervention to increase physical activity (walking –based intervention) but assuming no change in efficacy from the combined scenario analysis is reported in Table A8.8. It can be seen that this reduced the ICER by approximately half as the less intensive walking-based intervention has approximately half the cost of the structured leisure centre-based intervention which was used to estimate the cost of ERS in the combined scenario analysis.

Table A8.8: Sensitivity analysis applying intervention costs for a less intensive intervention to increase physical activity but assuming no reduction in efficacy.

	Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
ERS	£4,448	18.216	£101.2	0.007	£14,503
Usual care	£4,346	18.209			

The results of the threshold analysis on the cost of ERS were as follows. A 4% reduction in the cost of ERS from £229 to £220 gave an ICER just under £30,000 per QALY when holding all other conditions from the combined scenario analysis constant. A 36% reduction in the cost of ERS from £229 to £147 gave an ICER just under £20,000 per QALY when holding all other conditions from the combined scenario analysis constant.

A8.4 Conclusions

The ICER for the combined scenario analysis is £31,000 when using either the deterministic model or the PSA output. The application of the ITT data increased the ICER largely due its impact on the absolute QALY gains, but this was more than counteracted by the assumption that process utility gain would be accrued for up to 10 years with a linear fall-off in those remaining active being assumed.

The sensitivity analysis exploring the application of the EQ-5D utility data from the study by Murphy *et al* [29] shows that much larger QALY gains are estimated when applying the mean difference in utility between study arms rather than attributing a process utility gain only to those who become active. However, it should be noted that the EQ-5D difference measured by Murphy *et al*[29] was not statistically significant and this uncertainty hasn't been captured in the results

presented as there was insufficient time to run the PSA for this sensitivity analysis. Furthermore, in our clinical effectiveness review, some but not all of the studies which reported health related quality of life data found a statistically significant difference between ERS and usual care, suggesting that this short-term benefit is still relatively uncertain.

The threshold analysis on intervention cost and the sensitivity analysis applying a lower cost of ERS based on the cost of a walking-based intervention, both demonstrate that the ICER is sensitive to the cost of ERS. It should be noted that these analyses assume that there is no relationship between the cost of the scheme and its efficacy. It therefore cannot be concluded that lower cost schemes are more cost-effective unless it can also be shown that they are equally efficacious.

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