Title: The effect of exercise referral schemes upon health and wellbeing: Initial observational insights using individual patient data meta-analysis from The National Referral Database

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Abstract

Objectives: To examine if exercise referral schemes (ERS)s are associated with meaningful changes in health and wellbeing in a large cohort of individuals throughout England, Scotland, and Wales from The National Referral Database.

Methods: Data were obtained from 23,731 participants from 13 different ERSs lasting 6 weeks to 3 months. Changes from pre- to post-ERS in health and wellbeing outcomes were examined including body mass index (BMI), blood pressure (SBP & DBP), resting heart rate (RHR), short Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS), World Health Organization Well-Being Index (WHO-5), Exercise Related Quality of Life scale (ERQoL), and Exercise Self-Efficacy Scale (ESES). Two-stage individual patient data meta-analysis was used to generate effect estimates.

Results: Estimates [95%CIs] revealed statistically significant changes occurred compared to point nulls for BMI (-0.55 kg.m^2 [-0.69 to -0.41]), SBP (-2.95 mmHg [-3.97 to -1.92]), SWEMWBS (2.99 pts [1.61 to 4.36]), WHO-5 (8.78 pts [6.84 to 10.63]), ERQoL (15.26 pts [4.71 to 25.82]), ESES (2.58 pts [1.76 to 3.40]), but not RHR (0.22 f_c [-1.57 to 1.12]), DBP (-0.93 mmHg [-1.51 to -0.35]). However, comparisons of estimates [95%CIs] against null intervals suggested the majority of outcomes may not improve meaningfully.

Conclusions: We considered whether meaningful health and wellbeing changes occur in people who are undergoing ERSs? Regarding this broad question, these results demonstrate that, although many health and wellbeing outcomes improved, the changes be not achieve meaningful levels. This suggests the need to consider the implementation of ERSs more critically to discern how to maximize their effectiveness.

What is already known on this topic?

- Physical activity is widely considered to be effective in the prevention, management, and treatment of many chronic health disorders, yet population physical activity levels are relatively low and have changed little in recent years.
- Sufficient physical activity levels for health and wellbeing often do not arise as result of typical activities of daily living and thus, specific exercise has been argued to be necessary for many, and one approach to providing this has been through exercise referral schemes.
- These are aimed at increasing physical activity levels in sedentary individuals with chronic disease, however, evidence is currently lacking as to whether exercise referral schemes are effective as currently implemented.

What this study adds

- Our findings suggest that, though exercise referral schemes are associated with statistically significant changes in most health and wellbeing outcomes, the size of the changes was not as clinically meaningful as would be hoped for.
- These findings support the need to consider exercise referral schemes, and particularly their implementation, more critically using real world data to understand how best to maximise their potential, particularly considering the known benefits of exercise, and the reach of ERSs across the UK.

Introduction

Engagement in physical activity is widely considered to be effective in the prevention, management, and treatment of many chronic health disorders.[1,2] Despite this, in the United Kingdom (UK) a recent survey has shown that population levels of physical activity have remained unchanged in recent years, with a large proportion of the population still classed as inactive presenting potentially serious repercussions for population health.[3] The costs of physical inactivity to the National Health Service (NHS) were estimated as £900 million in 2015 [4] which, despite relatively stable levels of physical activity, had risen to £1.2 billion in 2017.[5] Though it is hoped that population wide increases in physical activity are possible they are difficult to achieve and thought to require complex interventions aimed at several socio-ecological levels.[6-9] Therefore it has been argued that the promotion of physical activity must be a key component of a healthcare system within a 'whole systems approach'.[10]

For many, achievement of sufficient levels of physical activity evidently does not arise from their typical activities of daily living in our present socio-ecological environment. Instead, as opportunities for spontaneous physical activity during daily life have likely reduced in our modern environment despite our bodies still 'expecting' this stimulus, directed *exercise* [11][a] may be a necessity for health and fitness in this current era.[1] Indeed, compared with replacing sedentary activity with just light physical activity, structured exercise may have differential effect health effects.[12] Further, for many conditions, network meta-analyses have shown exercise interventions are similarly, and in some cases more, effective than drug treatments for secondary prevention.[13,14] In this respect, it has been argued that exercise should perhaps be prescribed to patients much like a drug,[15] and as noted may be similarly effective.[12] Further, for some, recommendation from a physician/general practitioner (GP) may be a key facilitator in participating in exercise in the first place.[16]

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[a] It is worth differentiating *physical activity* from *exercise* here. Physical activity has been adopted as a term for those activities which are unstructured and occur as a result of tasks of daily living, occupation, or leisure without the explicit goal of improved health and/or fitness whereas exercise, though falling under the broad category of physical activity, involves tasks often specifically engaged in for the pursuit of improved health and/or fitness.[11] Both may present potential disturbances to homeostasis as a result of muscular action thus providing stimulus for adaptation including improved health and fitness.[11]

Considering a ‘whole systems approach’, where physical activity is argued to be a key component,[10] management and treatment of chronic diseases with exercise has been built into public health pathways and healthcare models through the use of exercise referral schemes (ERS). In ERS primary care professional, most commonly a GP, will refer a patient with, or at risk of, a chronic health disorder, into an exercise based intervention.[17,18] ERS were first introduced in the 1990s in primary care settings to facilitate exercise participation in those suffering from chronic disease.[19,20] Delivery of ERS usually occurs through leisure/sport centre pathways and often includes both cardiorespiratory and resistance training modalities, though despite typically poor reporting of the specific exercise intervention employed there is likely considerable heterogeneity in programme implementation.[17,18] ERS typically last from 10-12 weeks in England and Ireland,[18] or 16 weeks in Wales, the latter of which has been shown as more cost effective.[21]

Considering the current issues with the extant literature regarding ERS including inconsistent and weak evidence regarding their effects upon health, wellbeing, and quality of life outcomes [17,18,22,23] there is a need for continued evaluation to help inform guidelines regarding them.[17,24] Recent updated systematic review has highlighted that ERSs in the UK may be effective and that longer schemes may be more so than shorter schemes.[25] However, most schemes focus upon physical activity changes solely likely considering them appropriate surrogates for improved health and wellbeing. As such, it has been argued that ERS, and evaluation of their benefits, should extend beyond merely increasing physical activity levels and consider other health and wellbeing outcomes.[26] Thus the aim of this paper is to describe the initial insights obtained from individual patient data meta-analysis of The National Referral Database [27] with a primary focus on the effects (i.e. change from pre- to post-ERS), including point estimates and precision of those estimates, of ERSs upon health and wellbeing outcomes.

Methods

Study Design

An accompanying pre-print manuscript [27] describes the database formation, data cleaning, and structure in detail in addition to the key issues and limitations of the database. For sake of space this is not replicated here but the reader is encouraged to refer to this pre-print [27] to interpret the findings presented in their appropriate context. In essence, this database represents a retrospective cohort longitudinal study design following individuals entering and exiting ERS following referral from a range of organisations and referrer types (primary, secondary, and tertiary) across the UK. The database includes ERSs broadly speaking and unfortunately at present data is unavailable regarding their specific delivery, though work is underway to retrospectively determine details of this conforming to current reporting standards and described in Steele et al.[27] Due to the inclusion of different schemes within the database with varying and unspecified characteristics we used individual patient data meta-analysis with a two stage approach to account for this in analysis in providing point estimates and precision.

Outcome Measures

Outcome measures varied across the ERS but were taken at both pre- and post-intervention across all ERS. The majority of schemes included height and weight and from this body mass index (BMI) could be calculated. Blood pressure,[28] systolic (SBP) and diastolic (DBP), and resting heart rate were also included as outcomes in the majority of schemes. Mental wellbeing was included and measured in a small number of ERS using the short Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS) [29] and general wellbeing and quality of life using the World Health Organization Well-Being Index (WHO-5),[30] and Exercise Related Quality of Life scale (ERQoL).[31] Lastly, exercise related self-efficacy was collected in one scheme using the Exercise Self-Efficacy Scale (ESES).[32]

Statistical Analyses

Two stage individual patient data meta-analysis was performed on the change scores (i.e. post- minus pre-ERS scores) for each outcome measure. For stage one, change scores and their standard errors were derived for each scheme. For all measures, change scores were calculated in their raw units of measurement. The second stage involved performing a random effects meta-analysis using the 'metafor' package in R (version 3.5.0; R Core Development Team, https://www.r-project.org/) across all schemes in order to derive a final point estimate and precision of estimates (95% confidence intervals [CI]). Estimates were weighted by inverse sampling variance and restricted maximal likelihood estimation was used in all models. Schemes without sufficient participants ($n < 4$) were excluded from analysis in order to maintain sufficient sample sizes for precision of a one sample effect estimate calculated at 1 σ unit for the margin of error (or 95% confidence interval half width; ESCI 10-13, La Trobe University, Australia). Robustness of main effects were considered through sensitivity analyses by removal of individual schemes and re-analysis of the random effects model. Where significant estimates became non-significant and vice versa, in addition to where there were considerable changes in the magnitude and/or precision of those estimates, the results of sensitivity analyses are reported. Although initially intended, the effects of scheme length as a moderator were not examined due to the inclusion of only one scheme 6 weeks in length. It was considered that the slight difference between 12 weeks and 3 months (6 days) was unlikely to have any meaningful impact upon the analysis and any statistically significant findings might arise from type I errors.

Where it was possible to use an informed null interval, for each outcome measure we also calculated second generation *p* values [33] as supplementary statistics for the point estimate and precision of estimate of the random effects meta-analysis. The null interval for changes in each outcome were as follows: BMI = -1 to +1 kg.m^2 [34]; RHR = -5 to +5 f_c [35]; SBP & DBP = -2 to +2 mmHg [28]; WHO-5 = -10 to +10 pts [30]; SWEMWBS = -2.77 to +2.77 pts [36]. These null intervals were plotted onto forest plots for visual interpretation. Published data regarding either minimal clinically important changes, reliability etc. were not available for ERQoL or ESES and so second generation *p* values were not calculated for these outcomes.

An α level of 0.05 was used to determine statistical significance, however results were not interpreted dichotomously based purely on this, or whether the 95%CIs crossed zero. As noted, supplementary statistics in the form of second generation *p* values (p_δ) were also calculated to determine the proportion of data supported hypotheses that fall outside the null interval determined by the MCICs where a value of 1 suggested the data support only null hypotheses (i.e. no meaningful change in outcome), a value of 0 suggests the data support only alternative hypotheses (i.e. a meaningful change in outcome), and a value between these suggests the data are inconclusive at this stage (i.e. the possibility of both meaningful or non-meaningful changes are supported by the data). In essence, p_δ described the degree of overlap between the interval estimate (95%CIs) for the changes in outcome measures with the null intervals (MCICs) noted above. That is to say the analyses performed were with the intention of reporting broadly; do we observe a meaningful effect in people who are undergoing ERSs?

Additional supplemental meta-regression analyses were conducted to examine the association between changes in physical activity levels and changes in health and wellbeing outcomes. The results of these supplementary analyses are reported in the supplementary materials.

Results

Table 1 shows the final samples included in analysis. Table 2 shows the pre-ERS scores across the schemes for each of the outcome measures examined. Results from the supplementary meta-regressions are reported in the accompanying supplementary materials).

Body Mass Index

For BMI one scheme was excluded due to small sample size (scheme 5028) and a total of 11 schemes including 4,834 participants were included for analysis. Change in BMI differed significantly from the point null of zero (-0.55 kg.m^2 [-0.69 to -0.41], $p < 0.0001$). Figure 1 shows the forest plot for BMI. Significant heterogeneity was evident among the schemes ($Q_{(10)} = 161.34$, $p < 0.001$; $I^2 = 96.5\%$), however, sensitivity analysis did not reveal any influential schemes. The second generation *p* value for the estimate from the random effects model meta-analysis was $p_\delta = 1.00$ due to the interval estimate being entirely within the null interval suggesting that the data supported only null hypotheses.

Resting Heart Rate

For RHR one scheme was excluded due to small sample size (scheme 5028) and a total of 9 schemes including 4,287 participants were included for analysis. Change in RHR did not differ significantly from the point null of zero (-0.22 f_c [-1.57 to 1.12], $p = 0.7448$). Figure 2 shows the forest plot for RHR. Significant heterogeneity was evident among the schemes ($Q_{(8)} = 185.46$, $p < 0.001$; $I^2 = 97.5\%$), however, sensitivity analysis did not reveal any influential schemes. The second generation p value for the estimate from the random effects model meta-analysis was $p_\delta = 1.00$ due to the interval estimate being entirely within the null interval suggesting that the data supported only null hypotheses.

Systolic Blood Pressure

For SBP two schemes were excluded due to small sample size (schemes 5028 and 5144) and a total of 11 schemes including 7,389 participants were included for analysis. Change in SBP differed significantly from the point null of zero (-2.95 mmHg [-3.97 to -1.92], $p < 0.0001$). Figure 3 shows the forest plot for SBP. Significant heterogeneity was evident among the schemes ($Q_{(10)} = 55.38$, $p < 0.001$; $I^2 = 89.26\%$), however, sensitivity analysis did not reveal any influential schemes. The second generation p value for the estimate from the random effects model meta-analysis was $p_\delta = 0.039$ due to the interval estimate being only partly overlapped with the null interval suggesting that the majority of data supported hypotheses are that SBP decreases meaningfully, though the data are not wholly conclusive.

Diastolic Blood Pressure

For DBP two schemes were excluded due to small sample size (schemes 5028 and 5144) and a total of 11 schemes including 7,451 participants were included for analysis. Change in DBP differed significantly from the point null of zero (-0.93 mmHg [-1.51 to -0.35], $p = 0.0016$). Figure 4 shows the forest plot for SBP. Significant heterogeneity was evident among the schemes ($Q_{(10)} = 48.25$, $p < 0.001$; $I^2 = 85.39\%$), however, sensitivity analysis did not reveal any influential schemes. The second generation p value for the estimate from the random effects model meta-analysis was $p_\delta = 1.00$ due to the interval estimate being entirely within the null interval suggesting that the data supported only null hypotheses.

Short Warwick Edinburgh Mental Wellbeing Scale

A total of 3 schemes including 1,625 participants were included for analysis. Change in SWEMWBS differed significantly from the point null of zero (2.99 pts [1.61 to 4.36], $p < 0.0001$). Figure 5 shows the forest plot for SWEMWBS. Significant heterogeneity was evident among the schemes ($Q_{(2)} = 11.04$, $p < 0.001$; $I^2 = 77.97\%$). Sensitivity analysis did not reveal any influential schemes with respect to altering whether the estimate statistically significantly differed (i.e. shifted from significant to non-significant). Removal of scheme 5002 resulted in an increase in estimate to 3.81 [2.73 to 4.89]. The second generation *p* value for the estimate from the random effects model meta-analysis was $p_\delta = 0.422$ due to the interval estimate being overlapped with the null interval suggesting that the data are inconclusive. When scheme 5002 was removed this was reduced to $p_\delta = 0.018$ due to the interval estimate being only partly overlapped with the null interval suggesting that the majority of data supported hypotheses are that SWEMWBS increases meaningfully, though the data are not wholly conclusive. Considering the weighting of scheme 5002 in the random effects model meta-analysis it seems more likely that the original estimate and confidence intervals including all schemes is a better estimate of the true effect.

World Health Organization Well-being Index

Only one scheme (5131) collected the WHO-5 as an outcome measure and included 449 participants. Point estimate for change in WHO-5 score was 8.78 pts [6.84 to 10.63]. The second generation *p* value for the estimate was $p_\delta = 0.834$ due to the interval estimate being only partly overlapped with the null interval suggesting that the majority of data supported hypotheses are that null, though the data are not wholly conclusive.

Exercise Related Quality of Life scale

For ERQoL one scheme was excluded due to small sample size (scheme 5119) and a total of 3 schemes including 777 participants were included for analysis. Change in ERQoL differed significantly from the point null of zero (15.26 pts [4.71 to 25.82], p =0.0046). Figure 6 shows the forest plot for ERQoL. Significant heterogeneity was evident among the schemes ($Q_{(2)}$ = 254.21, p < 0.001; I^2 = 99.1%). Sensitivity analysis did not reveal any influential schemes with respect to altering whether the estimate statistically significantly differed (i.e. shifted from significant to non-significant). However, removal of scheme 5156 resulted in a reduction in the point estimate but an increase in the precision (9.83 pts [8.70 to 10.95], p < 0.001).

Exercise Self Efficacy Scale

Only one scheme (5131) collected the ESES as an outcome measure and included 252 participants. Point estimate for change in ESES score adjusting for pre-ERS score was 2.58 pts [1.76 to 3.40].

Discussion

Despite widespread adoption, research exploring the effect of ERSs on health outcomes from ecologically valid datasets is scarce. The results presented here describe the initial findings from first analysis of the National Referral Database; a UK wide database of ERS based on the Standard Evaluation Framework for physical activity interventions. The analyses performed here were with the intention of considering broadly; do we observe a meaningful effect in people who are undergoing ERSs? The present results demonstrate that, although many health and wellbeing outcome changes are statistically significant when compared to point null estimates (i.e. they differ from a change of zero) our analysis revealed a general lack of meaningful change over time in participants undergoing ERSs lasting between six weeks to three months.

For BMI our results suggested that the change over time was statistically significant, yet unlikely to be meaningful (-0.55 kg.m^2 [-0.69 to -0.41], p < 0.0001, p_δ = 1.0). This is perhaps unsurprising as physical activity or exercise based intervention as standalone approaches seem to lack effectiveness for eliciting changes in body mass [37]. Indeed, in their systematic review and meta-analysis, Pavey et al [18] reported no significant (or meaningful considering the criteria used here) differences in their meta-analysis of the effects of ERSs compared with other comparator interventions upon BMI. Studies of ERS ranging from eight weeks to four months show similarly little changes in BMI (i.e. ranging from no change to ~0.6 kg.m^2 [22,38-40]). Considering that participants undergoing ERSs in our sample were obese (BMI = 31.53±6.53 kg.m^2) lack of effectiveness could be considered an issue particularly as ERSs have been noted as being tied to the current 'obesity agenda'.[41] With the multiple lines of evidence suggesting that, alone, exercise may not result in meaningful weight loss, it may be argued that ERSs might benefit from combination with dietary guidance. There is perhaps potential here for wider social prescribing efforts regarding nutritional knowledge to coordinate with physical activity based interventions such a ERSs. Particularly as a BMI classified as overweight or obesity, albeit a crude measure, is on a population level associated with all-cause mortality risk.[42] One explanation for the lack of effect observed here, could be that positive changes in body composition occurred resulting in similar BMI post ERS (decrease in body fat and increase in lean mass). Such results have been shown to occur with a supervised resistance training based ERSs [43] and so, despite the lack of meaningful change in BMI, participants in the ERSs examined here may have experienced positive changes in body composition. Indeed, the supplementary meta-regression performed revealed a significant positive coefficient for change in BMI with change in vigorous minutes as a moderator (0.47 kg.m^2 [0.18 to 0.76], p = 0.0013; see supplementary materials) whereas this was not the case for total MET-minutes, moderate minutes, walking minutes, or sitting minutes. This may reflect positive body composition changes as a result of increased vigorous activity.

Measures of cardiovascular health, including RHR and blood pressure, were common outcomes in many of the ERSs observed here. High RHR is known to be a risk factor for both cardiovascular and all-cause mortality [44] yet no change was observed over time in those participating in ERSs according to our analysis. Only one paper reporting the results of three small studies (n's ranged from 11 to 65) has reported changes in RHR from ERS and our data is supportive of these. Webb et al [40] reported point estimates ranging from +2.0 to -6.8 f_c as a result of an eight week ERS. Heart rate data from FitBit covering 150 billion hours of activity suggests that in those who are 55 years of age (similar to the sample in the current database), an increase of 180 minutes' physical activity is needed to see an improvement in RHR of around ~6.5 f_c.[45] Previous meta-analysis of controlled trials has also shown an average change after endurance training of -6 f_c.[46] As noted, the exact 'exercise prescription' for ERS observed here is unknown and so it is difficult to know whether the lack of change in RHR might result from the implementation of exercise components that lack efficacy (i.e. either of insufficient volume or intensity of effort), or indeed due to poor fidelity of their implementation.

The change in SBP reported here was statistically significant, although its clinical meaningfulness should be treated with caution (-2.95 mmHg [-3.97 to -1.92], $p < 0.0001$, $p_\delta = 0.039$). Recent network meta-analysis shows that structured exercise interventions can produce similar reductions in SBP compared with anti-hypertensive medications,[13] though their effect estimates were greater than those reported here (-4.84 mmHg [-5.55 to -4.13] across all populations). This may be due to interventions being examined in the context of randomized controlled trials as opposed to the observational data examined here from 'real-world' interventions. Reduction in SBP to a range of 120 to 124 mmHg may provide the greatest reductions in risk of cardiovascular disease and all-cause mortality, particularly if the reduction to this level is large.[47] The mean baseline SBP for participants in the database was 131.70±16.91 mmHg and thus considering the results of Bundy et al [47] highlighting that large SBP reductions produce the greatest mortality risk reduction, in combination with the small reduction reported here, it is unclear whether sufficient reduction might have occurred to have meaningfully reduced risk. Though other studies of ERSs also report reductions in SBP these are either similarly small (-2.84 mmHg [-6.57 to 0.82] and -3.53 mmHg [-7.31 to 0.25] [22]; -3.2 mmHg [-4.6 to 1.7] and -2.9 mmHg [-4.4 to 1.4] [38]) or variable in their point estimates (-6.1 to +4.8 mmHg [40]). This is perhaps unsurprising as meta-analysis [48] suggest reductions are small for endurance type exercise (-3.5 mmHg [-4.6 to -2.3) and dynamic resistance training (-1.8 mmHg [-3.7 to -0.011]). The exception to this appears to be isometric exercise which produced far larger reductions (-10.9 mmHg [-14.5 to -7.4] [48]) suggesting that this form of exercise should perhaps be incorporated into ERSs. Cornelissen and Smart [48] also reported that reductions in blood pressure may be greater in prehypertensive or hypertensive participants and so, considering also the results of the recent network meta-analysis by Bundy et al,[47] it could be that the typical participant referred to an ERS may be unlikely to benefit meaningfully from it.

A statistically significant reduction in DBP was observed, yet this was unlikely to be clinically meaningful (-0.93 mmHg [-1.51 to -0.35], $p = 0.0016$, $p_\delta = 1.00$). Though as noted, a reduction in SBP to a range of 120 to 124 mmHg may reduce cardiovascular and all-cause mortality risk,[47] recent evidence also suggests that, when SBP is in the range of 120 to 140 mmHg, a DBP of 70 to 80 mmHg is optimal for reduced morbidity and mortality risk.[49] Participants in the database had baseline DBPs at the high end of the optimal range on average (80.13±9.91 mmHg) and so the small reduction found here might be considered meaningful in context; yet, it is unlikely that such a dichotomous consideration is accurate. As with SBP, prior studies typically show either no effects, or very small and variable effects, upon DBP with ERSs (0.77 mmHg [-2.07,3.61] and 1.55 mmHg [-1.02,4.11] [22]; -2.5 mmHg [-3.5 to -1.5] and 0.2 mmHg [-3.8 to -0.8] [38]; -4.1 mmHg to 3.0 point estimates [40]). Again this is perhaps unsurprising given the small effects reported in meta-analysis [48] for endurance exercise (-2.5 mmHg [-3.2 to -1.7]) and dynamic resistance training (-3.2 mmHg [-4.2 to -2.0]), or combined training (-2.2 mmHg [-3.9 to -0.48]). Though again isometric exercise appears more effective than traditional approaches (-6.2 mmHg [-10.30 to -2.0]). Of course as noted, we were unable to consider the impact of different exercise approaches used within the ERSs examined here so again it may be that the relatively small change in DBP might result from the implementation of exercise components that lack efficacy (i.e. either of insufficient volume or intensity of effort).

Other outcomes included a variety of questionnaires relating to mental wellbeing, quality of life, and self-efficacy relating to exercise. Only three schemes examined SWEMWBS and though the improvement was statistically significant, initial analysis suggested that it was unclear as to whether the change was meaningful (2.99 pts [1.61 to 4.36], $p < 0.0001$, $p_\delta = 0.422$). Sensitivity analysis did reveal one influential scheme and removal of that scheme improved the estimated from meta-analysis (3.81 [2.73 to 4.89], $p < 0.0001$, $p_\delta = 0.018$). That scheme however was considerably larger than the other two included (n = 1,479 vs 107 and 39). Thus it is possible that the point estimate from this scheme is better representative of μ and indeed the 95%CIs are far narrower suggesting better precision of the estimate. Only one study to our knowledge has examined SWEMWBS specifically in response to exercise based intervention. Skinner et al [50] reported a point estimate for change in SWEMWBS of 1.5 pts [-1.0 to 4.0] after a short four week supervised exercise intervention once a week in prostate cancer survivors. Malcolm et al [51] used the full WEMWBS and reported a change of 3 pts [0.0 to 6.0] and, though both measure subtly different components of mental wellbeing, considering the relationship between both the SWEMWBS and WEMWBS [52] it seems as though this reflects a similar sized effect. Recent large scale observational research [53] highlights that physical activity is significantly and meaningfully associated with mental health (1.49 fewer days of poor mental health in the past month). However, RCT evidence from ERSs [54] would initially appear less supportive of a role for physical activity and exercise in mental health, in this case depression, though recent analysis suggests that many studies and media portrayals of the role of physical activity and exercise are misrepresented.[55] Other studies have shown reductions in anxiety and depression from ERSs in both those with and without prior mental health issues.[22,56] Despite a lack of agreement within the extant literature it would appear that physical activity and exercise can have positive effects upon mental health. Indeed, recent work shows that resistance training for example improves both anxiety and depressive symptoms regardless of prior health status,[57,58] and meta-analysis of broad exercise approaches for depression controlling for publication bias support an effect.[59] Our results suggest this effect may also be present in those undergoing ERSs, yet the clinical meaningfulness of the effect is less clear.

Global wellbeing and quality of life related outcomes were also explored in some ERS. One scheme collected the WHO-5 wellbeing-index where there was a statistically significant, yet likely not meaningful, change (8.78 pts [6.84 to 10.63], p_{δ} = 0.834]. Few studies have used the WHO-5 as an outcome measure,[30] though one has compared exercise to wake therapy in those with major depression [60] reporting a point estimate for improvement from exercise of 46 pts. A study in older adults performing a 6 months progressive high effort resistance training intervention [61] found an improvement of 7.26 pts [5.78 to 8.74]. It would seem that responsiveness of the WHO-5 to exercise based interventions may be at least in part dependent upon the population as large effects have been reported for major depression [60] whereas the effects reported for older adults,[61] and here in ERS participants, do not typically exceed the minimal clinically important change.[30] A relatively novel outcome measure designed specifically for evaluation of quality of life in those participating in ERSs [31] was also included in some schemes. Results from the meta-analysis suggested that there was a statistically significant improvement in this outcome (15.26 pts [4.71 to 25.82], p =0.0046), and that sensitivity analysis revealed an increase in the precision of estimate for the effect when one influential scheme was removed (9.83 pts [8.70 to 10.95], $p < 0.001$). However, though specifically designed for use with ERSs, this outcome lacks research regarding what constitutes a minimal clinically important change and so it is difficult to determine whether the improvements seen are indeed meaningful.

The final outcome examined, ESES, was only collected by one scheme. ESES showed a significant change of 2.58 pts [1.76 to 3.40], though the lack of prior literature examining this as an outcome measure makes it difficult to determine the meaningfulness of this change. Exercise interventions have been shown to improve general self-efficacy.[62] Further the extent to which self-efficacy is affected by an intervention may impact upon their ability to produce behaviour change (e.g. for web based health interventions [63]). It has also been shown that changes towards higher exercise self-efficacy predicts continuation of exercise behaviour once an intervention has ended.[64] Thus it might be that the results here suggesting an impact of ERS upon ESES might lead to longer term maintenance of behaviour.

As noted, currently there is a lack of agreement of what constitutes 'impact' with respect to the evaluation of ERS [41] and the evidence presented here from one of the largest databases of ERS does little to support the use of ERSs, broadly speaking. Though it should be noted that the database and analyses presented here are not without limitations (observational data without control group for counterfactual, follow-up bias due to high proportion of dropouts, selection of null intervals for meaningfulness of effects, details of specific components of ERS including fidelity, or consideration of participant characteristics such as referral reasons etc.) and these are detailed further in the accompanying manuscript describing the initial overview of the database.[27] Indeed, in considering factors such as lack of appropriate controls and follow up bias, it may be that the overall effects reported may be lesser in reality. However, given the considerable heterogeneity seen between schemes ($I^2 >$ 78% across outcomes) some schemes may be more effective than other due to characteristics either relating to the scheme specifically, or perhaps characteristics of the types of participants undergoing that scheme. Given that scheme level characteristics regarding delivery are not present available in this dataset, it is unfortunately difficult to explore the effects of personal level characteristics (e.g. BMI pre-ERS).

Conclusion

The data presented here represents the initial findings from first analysis of the National Referral Database health and wellbeing data. The analyses performed were with the intention of considering broadly “do we observe a meaningful effect in people who are undergoing ERSs?” and the findings revealed a general lack of meaningful change over time in participants undergoing ERSs lasting between six weeks to three months in length. These findings suggest the need to consider the implementation of ERSs more critically to discern how best to maximize their potential in light of the wider literature supporting the efficacy of physical activity and exercise, and the extensive reach of ERSs across the UK.

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Patient and Public Involvement

There was no patient or public involvement in the production of this research.

Data Sharing

All data is available upon request from the corresponding author and we would encourage researchers to consider broader questions that might be answered with this dataset and to contact us in this regard.

Ethics Statement

As per the Health Research Authority and Research Ethics Committee section 11 of Standard Operating Procedures, ethical approval is not required for research involving patient data that is not identifiable.

Transparency Statement

The guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Table 1. Characteristics of all schemes included in analysis.

Scheme Number	Age (Mean±SD)	*N* (% male)
5001	56±17	1264 (41.6%)
5002	48±12	3736 (24.7%)
5026	49±13	2070 (22.9%)
5036	51±15	3736 (27.9%)
5056	50±15	4574 (34.2%)
5063	45±11	325 (27.1%)
5072	48±12	1735 (25.9%)
5089	56±15	1670 (40.5%)
5108	51±16	591 (30.0%)
5115	57±14	853 (45.0%)
5131	50±16	1628 (39.5%)
5144	53±17	450 (39.8%)
5156	59±15	1099 (38.1%)
All schemes	51±15	23731 (31.8%)

Table 2. Pre-ERS scores for all outcome measures for each scheme included in analysis.

Scheme	BMI (kg.m^2)	RHR (f_c)	SBP (mmHg)	DBP (mmHg)	WHO-5 (pts)	SWEMWBS (pts)	ERQoL (pts)	ESES (pts)
5001	27.90±5.66	72.70±9.32	127.80±15.09	78.91±9.54	N/A	N/A	N/A	N/A
5002	33.56±5.67	76.74±10.40	130.20±17.10	81.18±9.83	N/A	23.75±5.32	N/A	N/A
5026	30.95±6.23	77.33±11.50	129.00±16.73	79.75±9.40	N/A	N/A	N/A	N/A
5036	31.60±6.53	76.20±11.41	134.60±16.06	81.41±9.56	N/A	N/A	N/A	N/A
5056	30.78±6.00	76.13±10.96	130.50±17.72	77.76±10.42	N/A	N/A	N/A	N/A
5063	31.63±4.89	71.67±10.86	132.10±10.87	80.86±6.44	N/A	23.25±5.74	N/A	N/A
5072	35.13±6.80	68.54±8.49	134.20±16.88	81.35±9.80	N/A	N/A	N/A	N/A
5089	32.46±7.26	N/A	134.40±15.30	81.29±9.17	N/A	N/A	N/A	N/A
5108	30.63±6.66	71.90±10.42	131.30±18.63	83.39±9.17	N/A	N/A	70.47±12.42	N/A
5115	N/A	N/A	N/A	N/A	N/A	23.68±4.17	N/A	N/A
5131	25.64±4.11	N/A	126.00±16.34	78.21±9.43	40.86±20.70	N/A	N/A	30.94±5.89
5144	30.35±5.33	N/A	127.00±4.24	77.50±10.61	N/A	N/A	74.49±12.44	N/A
5156	N/A	76.55±9.43	134.1±16.38	79.68±9.37	N/A	N/A	56.44±14.19	N/A
All schemes	31.53±6.53	75.81±10.76	131.70±16.91	80.13±9.91	40.86±20.70	23.72±5.33	62..37±15.32	30.94±5.89

Figure titles

Figure 1. Forest plot of change in BMI across schemes. Note: dashed red lines represent the MCIC derived null intervals for interpretation of the meaningfulness of changes.

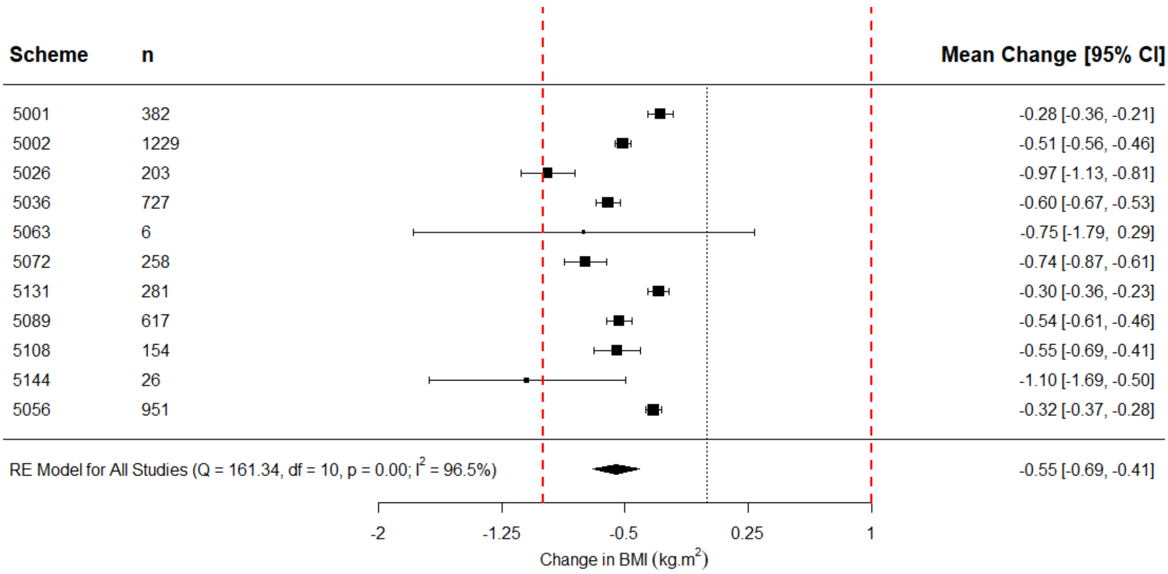
Figure 2. Forest plot of change in RHR across schemes. Note: dashed red lines represent the MCIC derived null intervals for interpretation of the meaningfulness of changes.

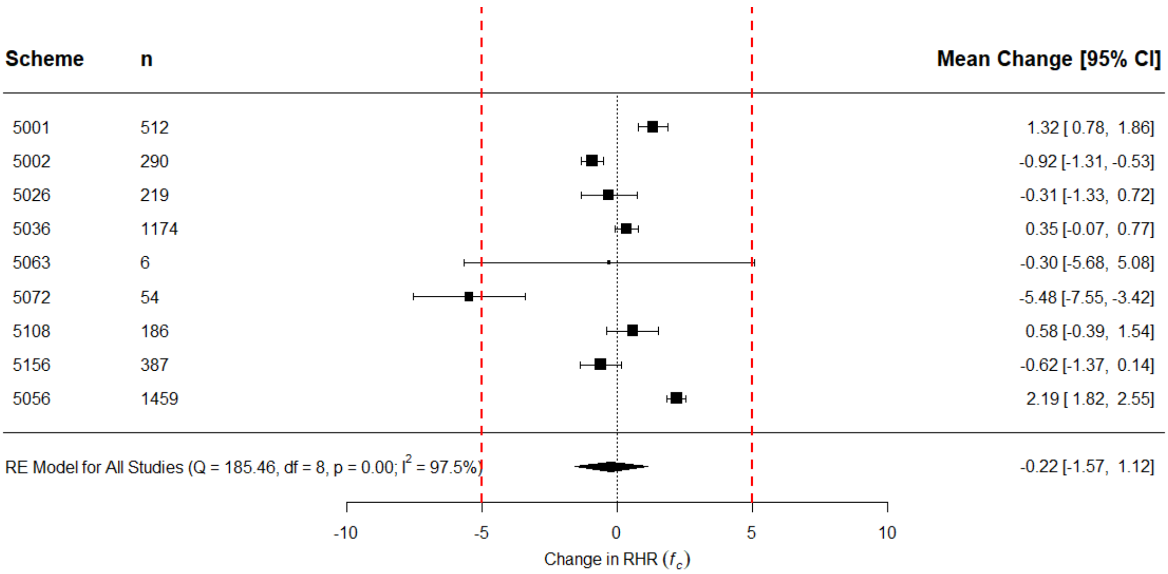
Figure 3. Forest plot of change in SBP across schemes. Note: dashed red lines represent the MCIC derived null intervals for interpretation of the meaningfulness of changes.

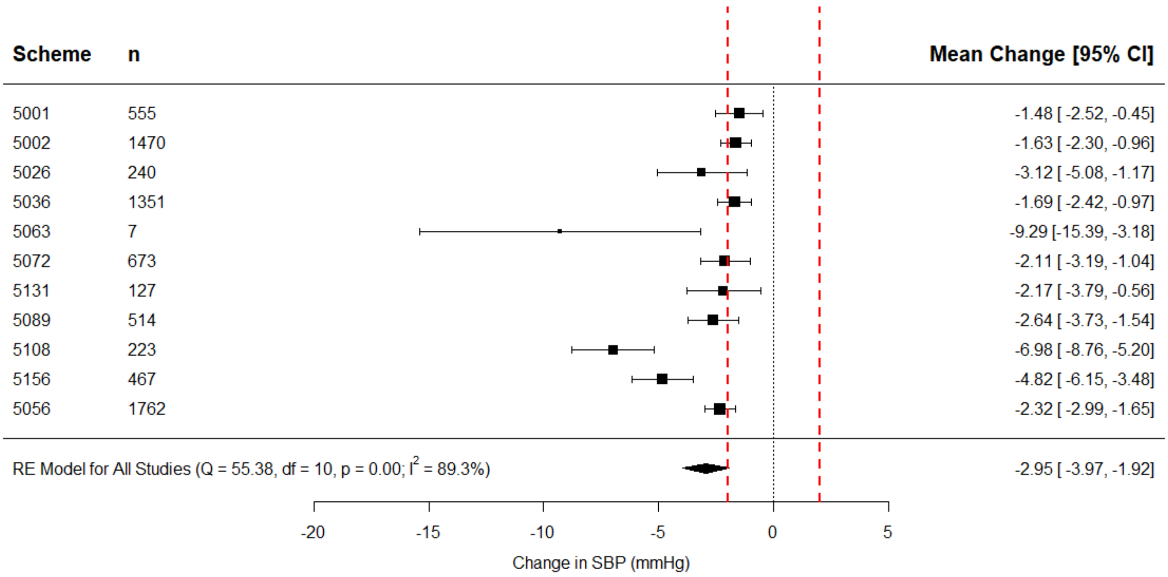
Figure 4. Forest plot of change in DBP across schemes. Note: dashed red lines represent the MCIC derived null intervals for interpretation of the meaningfulness of changes.

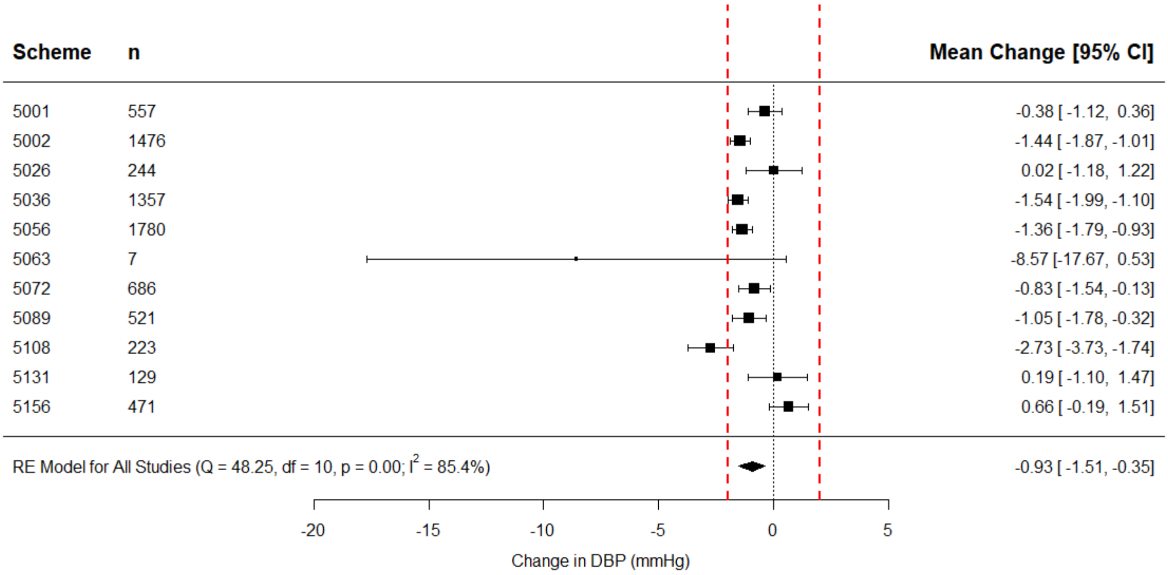
Figure 5. Forest plot of change in SWEMWBS across schemes. Note: dashed red line represents the MCIC derived null intervals for interpretation of the meaningfulness of changes.

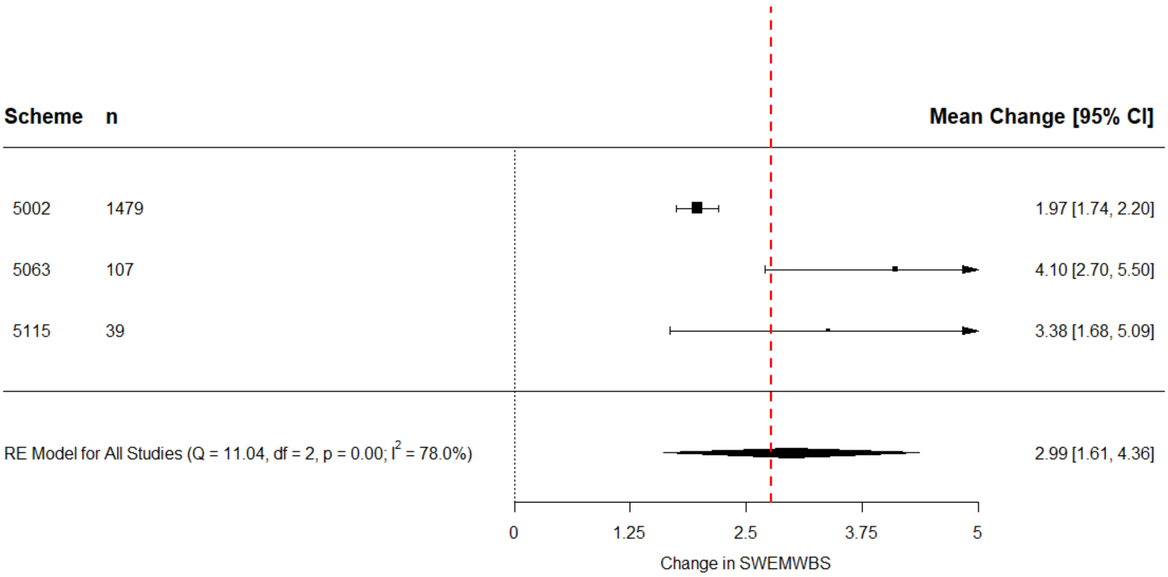
Figure 6. Forest plot of change in ERQoL across schemes.

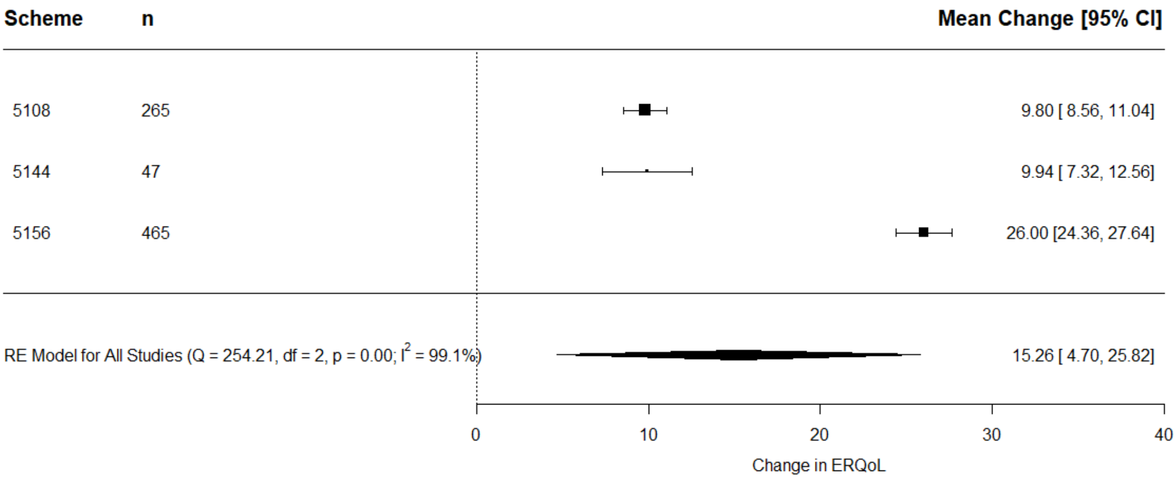

Scheme
n
Mean Change [95% CI]
5001 382 -0.28 [-0.36, -0.21]
5002 1229 -0.51 [-0.56, -0.46]
5026 203 -0.97 [-1.13, -0.81]
5036 727 -0.60 [-0.67, -0.53]
5063 6 -0.75 [-1.79, 0.29]
5072 258 -0.74 [-0.87, -0.61]
5131 281 -0.30 [-0.36, -0.23]
5089 617 -0.54 [-0.61, -0.46]
5108 154 -0.55 [-0.69, -0.41]
5144 26 -1.10 [-1.69, -0.50]
5056 951 -0.32 [-0.37, -0.28]
RE Model for All Studies (Q = 161.34, df = 10, p = 0.00; I² = 96.5%) -0.55 [-0.69, -0.41]
-2
-1.25
-0.5
0.25
1
Change in BMI (kg.m²)


Scheme
n
Mean Change [95% CI]
5001 512 1.32 [0.78, 1.86]
5002 290 -0.92 [-1.31, -0.53]
5026 219 -0.31 [-1.33, 0.72]
5036 1174 0.35 [-0.07, 0.77]
5063 6 -0.30 [-5.68, 5.08]
5072 54 -5.48 [-7.55, -3.42]
5108 186 0.58 [-0.39, 1.54]
5156 387 -0.62 [-1.37, 0.14]
5056 1459 2.19 [1.82, 2.55]
RE Model for All Studies (Q = 185.46, df = 8, p = 0.00; I² = 97.5%) -0.22 [-1.57, 1.12]
-10
-5
0
5
10
Change in RHR (f_c)


Scheme
n
Mean Change [95% CI]
5001 555 -1.48 [-2.52, -0.45]
5002 1470 -1.63 [-2.30, -0.96]
5026 240 -3.12 [-5.08, -1.17]
5036 1351 -1.69 [-2.42, -0.97]
5063 7 -9.29 [-15.39, -3.18]
5072 673 -2.11 [-3.19, -1.04]
5131 127 -2.17 [-3.79, -0.56]
5089 514 -2.64 [-3.73, -1.54]
5108 223 -6.98 [-8.76, -5.20]
5156 467 -4.82 [-6.15, -3.48]
5056 1762 -2.32 [-2.99, -1.65]
RE Model for All Studies (Q = 55.38, df = 10, p = 0.00; I² = 89.3%) -2.95 [-3.97, -1.92]
-20
-15
-10
-5
0
5
Change in SBP (mmHg)


Scheme
n
Mean Change [95% CI]
5001 557 -0.38 [-1.12, 0.36]
5002 1476 -1.44 [-1.87, -1.01]
5026 244 0.02 [-1.18, 1.22]
5036 1357 -1.54 [-1.99, -1.10]
5056 1780 -1.36 [-1.79, -0.93]
5063 7 -8.57 [-17.67, 0.53]
5072 686 -0.83 [-1.54, -0.13]
5089 521 -1.05 [-1.78, -0.32]
5108 223 -2.73 [-3.73, -1.74]
5131 129 0.19 [-1.10, 1.47]
5156 471 0.66 [-0.19, 1.51]
RE Model for All Studies (Q = 48.25, df = 10, p = 0.00; I² = 85.4%) -0.93 [-1.51, -0.35]
-20
-15
-10
-5
0
5
Change in DBP (mmHg)


Scheme
n
Mean Change [95% CI]
5002 1479 1.97 [1.74, 2.20]
5063 107 4.10 [2.70, 5.50]
5115 39 3.38 [1.68, 5.09]
RE Model for All Studies (Q = 11.04, df = 2, p = 0.00; I² = 78.0%) 2.99 [1.61, 4.36]
0
1.25
2.5
3.75
5
Change in SWEMWBS


Scheme
n
Mean Change [95% CI]
5108 265 9.80 [8.56, 11.04]
5144 47 9.94 [7.32, 12.56]
5156 465 26.00 [24.36, 27.64]
RE Model for All Studies (Q = 254.21, df = 2, p = 0.00; I² = 99.1%) 15.26 [4.70, 25.82]
0
10
20
30
40
Change in ERQoL