Evaluation of cardiovascular risk-lowering health benefits accruing from laboratory-based, community-based and exercise-referral exercise programmes

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ABSTRACT

Background: To evaluate the ability of community-based exercise programmes to facilitate public participation in exercise and hence improved cardiovascular health, we assessed the respective impacts of: a continuously monitored exercise programme based within our university (study 1); a Valleys Regional Park-facilitated community-based outdoor exercise programme (study 2); a Wales National Exercise Referral Scheme-delivered exercise-referral programme (study 3).

Methods: Biomolecular (monocytic PPARγ target gene expression), vascular haemodynamic (central/peripheral blood pressure, arterial stiffness), clinical (insulin sensitivity, blood lipids) and anthropometric (body mass index, waist circumference, heart rate) parameters were investigated using RT-PCR, applanation tonometry, chemical analysis and standard anthropometric techniques.

Results: In studies 1–3, 22/28, 32/65 and 11/14 participants adhered to their respective exercise programmes, and underwent significant increases in physical activity levels. Importantly, beneficial effects similar to those seen in our previous studies (eg, modulations in expression of monocytic PPARγ target genes, decreases in blood pressure/arterial stiffness, improvements in blood lipids/insulin sensitivity) were observed (albeit to slightly differing extents) only in participants who adhered to their respective exercise programmes. While study 1 achieved more intense exercise and more pronounced beneficial effects, significant cardiovascular risk-lowering health benefits related to biomolecular markers, blood pressure, arterial stiffness and blood lipids were achieved via community/referral-based delivery modes in studies 2 and 3.

Conclusions: Because cardiovascular health benefits were observed in all 3 studies, we conclude that the majority of benefits previously reported in laboratory-based studies can also be achieved in community-based/exercise-referral settings. These findings may be of use in guiding policymakers with regard to introduction and/or continued implementation of community/referral-based exercise programmes.

INTRODUCTION

Physical activity is a major factor in preventing/delaying onset of cardiovascular disease (CVD), and in increasing life expectancy and quality of life. However, only 30–60% of UK adults partake in recommended levels of physical activity. Therefore, there is an urgent need to implement accessible exercise programmes that can facilitate increased public participation in exercise. Similarly, where such programmes exist, there is a need to evaluate these programmes with regard to their abilities to alleviate CVD risk, and hence evaluate the benefits that such initiatives may bring to patients/participants, and more broadly to society as a whole.
We and others have reported that during exercise, certain signals are released from skeletal muscle into the circulation; reviewed in refs. 15 and 16. Thus, single exercise bouts have acute impacts on levels of blood-borne signals such as activators of the ligand-activated transcription factor PPARγ and on expression within circulating monocytes of target genes for these signals. Similarly, sustained changes in monocyte expression patterns of these target genes are seen in participants who have undergone exercise programmes involving regular exercise over periods of 8-8 weeks.

We have identified associations between such exercise-associated signalling effects and clinical parameters relevant to CVD risk: exercise-associated activation of PPARγ signalling correlates with improvements in insulin sensitivity, increased high-density lipoprotein (HDL) cholesterol, reduced arterial stiffness and reduced fasting plasma glucose. Thus, our previous studies have established a group of easily measured ‘biomarkers’ that may be used to evaluate the ability of exercise programmes to achieve CVD risk-lowering clinical outcomes.

However, because our previous studies invariably involved participants undertaking continuously monitored sessions in University laboratories under the constant supervision of researchers, we wished to carry out translational research evaluating whether the beneficial effects seen in our previous laboratory-based studies can also be demonstrated in exercise-referral/community-based interventions. In Wales (where the current study was based), the Valleys Regional Park (VRP) facilitates provision of community-based outdoor walking programmes to residents of the South Wales Valleys, while the Wales National Exercise Referral Scheme (NERS) standardises exercise referral opportunities across all Welsh Local Authorities/Health Boards.

However, although 68% of NERS participants are referred for CVD-related conditions, previous evaluations of NERS exercise programmes have been limited to adherence, quality of life, cost-effectiveness and mental health, while evaluation of VRP programmes has not been undertaken at all.

Therefore, to test the hypothesis that exercise-referral/community-based initiatives are a viable means of making exercise-associated health benefits accessible to a broad cross-section of the population, the current study aimed to evaluate the respective impacts of: (1) an in-house continuously monitored exercise programme; (2) a VRP-facilitated community-based outdoor exercise programme; (3) a NERS-delivered exercise-referral programme, with regard to the range of biomolecular, vascular haemodynamic, clinical and anthropometric parameters used in our previous studies.

**MATERIALS/METHODS**

**Study I:** Twenty-eight healthy participants (age 44.6±11.4 years; 89% females/11% males; 95% Caucasian), deemed to lead sedentary lifestyles following completion of International Physical Activity Questionnaires (IPAQs), were recruited from staff/students of Cardiff Metropolitan University. Exclusion criteria were a history of cardiovascular/metabolic disorders, a physically active lifestyle (ie, taking part in structured exercise three times or more per week), pregnancy or taking CV-acting medications.

Initially, participants’ maximal oxygen consumption (VO2max) was estimated using Rockport fitness walking tests; participants then completed 3×45 min monitored treadmill-walking sessions each week for a total of 24 sessions (10 000 steps per session). Throughout the 8-week programme, heart rate was monitored, and the speed at which participants walked was adjusted according to changes identified in their heart rate (ie, pace was increased as heart rate decreased/plateaued) in order to maintain a constant ‘moderate’ intensity (66.6±1.37% of maximal heart rate (defined as [220−participant age]) or approximately 60% VO2max).

Measurements were taken at baseline (week 0) and on completion (week 8) of the programme. Consultations took place under fasting conditions (no food consumption on the day of testing); participants had not consumed alcohol/caffeine or carried out any strenuous exercise in the previous 24 h. Participants completed a lifestyle/dietary questionnaire during each consultation; no significant changes in lifestyle/diet were observed over the period of the intervention.

**Anthropometric measures:** Body mass, body mass index (BMI), waist circumference and heart rate were measured using standard protocols. Peripheral blood pressure (BP) was measured on the non-dominant arm, according to European Society of Hypertension guidelines.

**Collection of blood samples:** Whole blood was obtained by venepuncture of the antecubital vein and collected in EDTA and serum separator vacuum tubes for collection of leucocytes and serum samples, respectively, as previously described. Monocytes were obtained from leucocyte samples using commercial monocyte-isolation columns (QuadroMACS separator units, LS columns and CD14 MicroBeads (Miltenyi Biotec, Bisley, UK)) according to the manufacturers’ instructions. RNA was obtained from monocyte samples, converted to cDNA and used in Fast-SYBRGreen (Applied Biosystems, Paisley, UK) or Taqman Primetime (Integrated DNA Technologies Inc, Iowa, USA) PCR-based gene expression assays as previously described.

Oligonucleotide primers (Sigma, Poole, UK) were: ATP-Binding Cassette protein A1 (ABCA1): F: 5′ GCACTGGAAGATGCTG AAA 3′; R: 5′ AGTTCCCTGGAAGGTCTTGTTCA 3′; cluster of differentiation isoform-36 (CD36): F: 5′ GGAGATGTAGTGAACGACGAC 3′; R: 5′ GAGACTGTGT TTGTCTTCAGGCT 3′; matrix metalloproteinase-9 (MMP-9): ‘Taqman Primestime’ code Hs00234579_m1; β-actin (‘housekeeper gene’ #1): ‘Taqman Primestime’ code 4310881E-1404039; GAPDH (‘housekeeper gene’ #2): F: 5′ CATTGACCTAACATACATG 3′; R: 5′ TCCCATGGTGGTGAAGAC 3′.
Analysis of serum samples: Serum fasting insulin levels were determined using an Invitrogen Insulin Assay Kit (both Invitrogen Ltd, Paisley, UK). An iLab V.300 Plus clinical chemistry analyser (Instrumentation Laboratoryies UK Ltd, Warrington, UK) was used to quantify fasting glucose, total and HDL-cholesterol, and triglycerides, within serum samples. Serum low-density lipoprotein (LDL) levels were calculated using the Friedewald equation. Insulin sensitivity was quantified using the homeostatic model assessment formula.

Study 2: Sixty-five participants (age 44.5±2.5 years; 85% females/15% males; 98% Caucasian) who had expressed an interest (independently of this study) in joining community-based twice-weekly outdoor walking groups set up as affiliates of VRP were recruited. Inclusion/exclusion criteria, ethical considerations, anthropometric measurements, blood sample collection, serum analysis, RNA extraction and PCR-based gene expression assays were all as for study 1. As for study 1, participants completed a lifestyle/dietary questionnaire during each consultation, and no significant changes in lifestyle/diet were observed over the period of the intervention. However, the following aspects of study 2 were distinct in nature from study 1.

Green exercise
The study was carried out in the South Wales Valleys, an area of high social and economic deprivation, low physical activity levels and vascular haemodynamics is being employed as a method of combating low physical activity and poor health in the South Wales Valleys, by engaging people with exercise in their local area/environment. The walks took place in rural/countryside settings, and as such constituted ‘green exercise’ (ie, any exercise that takes place in a relatively natural setting). Physical activity levels undertaken during each walk were quantified using accelerometer arm bands (BodyMedia SenseWear, Pennsylvania, USA).

Vascular haemodynamic measurements
Augmentation Index (AIx, an indirect measure of systemic arterial stiffness) and aortic pulse wave velocity (aPWV, the ‘gold standard’ measure of large artery stiffness) were recorded non-invasively using applanation tonometry (SphygmCor, Atcor Medical, Sydney, Australia). Recording the radial pulse wave enabled reconstruction and pulse wave analysis of the central aortic pulse waveform (and hence, determination of central systolic BP and diastolic BP) using a generalised transfer function. aPWV was measured as the velocity of the pulse wave as it travels along the aorta, as previously described. Determination of path length was calculated using a tape measure between the suprasternal notch and both carotid and femoral artery sites. aPWV data were normalised to the mean arterial pressure (mean arterial pressure-adjusted carotid-femoral aPWV), while AIx data were normalised to heart rate (AIx at HR75 bpm).

Study 3: Fourteen participants (age 56.0±3.9 years; 50% females/50% males; 100% Caucasian), who had been referred to 16-week leisure centre-based NERS exercise programmes, were recruited (NB: to aid comparison with studies 1 and 2, sampling was carried out at weeks 0 and 8 of this programme). This cohort’s age is in line with previous NERS evaluations (age 52±15 years), which suggests that the cohort was representative of NERS participants as a whole. The exercise programme comprised twice-weekly 35 min group exercise sessions (walking-based gym sessions; NERS patients only) that were professionally supervised by a NERS ‘exercise professional’.

Inclusion and exclusion criteria, anthropometric measurements, blood sample collection, serum analysis, RNA extraction and PCR-based gene expression assays were as for studies 1 and 2, with the exception of the study’s main inclusion criterion: participants had to have been referred by their general practitioner (GP) to NERS for conditions that had raised CVD risk (eg, ‘prediabetes’ diagnoses [impaired glucose tolerance and/or increased fasting glucose], obesity, hypertension). As for study 1, participants completed a lifestyle/dietary questionnaire during each consultation; no significant changes in lifestyle/diet were observed over the period of the intervention. Finally, measurement of physical activity levels and vascular haemodynamics was carried out as for study 2.

Ethical considerations
In all three cases, the studies conformed to the principles outlined in the Declaration of Helsinki: all participants completed informed consent forms, and ethical approval was granted by either the Cardiff Metropolitan University faculty of Health Science Research Ethics Committee or the UK National Health Service (NHS) Integrated Research Application System.

Statistical analysis
All data were expressed as mean±SEM; paired t tests and analyses of variance were used to compare differences between two-sample and multiple data sets, respectively. Correlation analyses (using Pearson’s method) were also carried out, with ‘Δ changes’ (ie, differences between measurements taken pre-exercise at weeks 0 and 8 of the intervention) used as source data for these analyses. Statistical analyses were performed using Minitab16 and/or SPSS software, with results deemed significant at p<0.05.

RESULTS
Levels of physical activity/adherence. Study 1’s exercise programme was explicitly defined as 30 000 steps/week, undertaken as 3×45 min sessions. Adherence was ensured by continuous monitoring by researchers;
participants who failed to attend or complete a session were excluded from the remainder of the study. Of the original 28 participants, 6 were excluded for this reason; data from only the remaining 22 participants are included in this manuscript.

For study 2, registers of attendance, taken throughout the programme to determine the adherence of each participant, demonstrated that not all participants attended all walks. Adherence to exercise programmes is commonly defined as attendance of at least 70% of sessions; based on this, the cohort was split into two subgroups: those who adhered to the programme (n=32), and those who did not adhere (n=33). Accelerometer data identified that participants within the adherent group were physically active for 34±3 min per session (during which the intensity of the exercise undertaken was 3.58±0.06 metabolic equivalent of tasks (METs), which corresponds to a moderate intensity), and achieved 868±236 steps/week in addition to their normal lifestyles (p<0.001, paired t test vs week 0). The non-adherent group’s physical activity levels remained constant, while the adherent group’s physical activity levels underwent a significant increase of 296±29 IPAQ MET-mins/week (p<0.001, paired t test vs week 0).

For study 3, registers showed that 11/14 participants attended their prescribed exercise sessions (and also their consultation sessions with researchers); the 3 participants who did not attend were excluded from the remainder of the study. Accelerometer data demonstrated that participants achieved 3486±469 additional steps/week (p<0.05, paired t test vs week 0), and 4.66±0.18 additional METs/week or 98±142 additional IPAQ MET-mins/week, respectively, corresponding to non-significant 10–30% increases in weekly physical activity (p<0.05, paired t test vs week 0).

Biomolecular measurements: In study 1 participants, and in the adherent group from study 2, CD36 and ABCA1 (which are positively regulated by exercise-associated signalling stimuli) underwent significant approximately twofold to threefold increases in expression (p<0.05 in both cases; see table 1). Similarly, in study 3, non-significant 1.9-fold and 1.4-fold trends towards increased expression were observed (p<0.05 in both cases). Conversely, MMP-9 (which is negatively regulated by exercise-associated signalling stimuli) underwent decreases in expression which either attained or approached statistical significance (p<0.01 for study 1 and the adherent group from study 2; p=0.07 for study 3).

Vascular haemodynamic measurements: As expected, study 3 participants (who had been referred to NERS following diagnosis of conditions that had raised CVD risk) exhibited significantly higher baseline readings with regard to several vascular haemodynamic parameters than did the healthy sedentary participants from the other studies (see table 2). Nevertheless, in all three studies, exercise participation was associated with significant reductions in peripheral BP (p<0.05; see table 1). Arterial stiffness (as measured by AIX) decreased significantly in study 3 and the adherent group from study 2 (p<0.05 and <0.01, respectively), and a borderline-significant decrease (p=0.07) in aPWV was seen in study 3, but not in study 2.

Anthropometric and clinical measurements: Baseline BMI data for all studies were in the ‘obese’ or ‘overweight’ range, which can be considered a cardiovascular risk factor. Nevertheless, participants from study 3 (who had been referred to NERS specifically because of diagnosis with raised CVD risk) exhibited significantly higher baseline readings with regard to waist circumference (p<0.01), circulating levels of glucose (p<0.001), total cholesterol (p<0.01) and LDL-cholesterol (p<0.01) than did the participants from the other studies (see table 2).

The most pronounced exercise-associated improvements in beneficial anthropometric and clinical parameters (ie, improvements in weight, BMI, waist circumference, fasting insulin levels and insulin sensitivity) were seen in study 1. As study 1 involved the greatest physical activity levels, this suggests that study 1’s intensity reached the threshold required to achieve improvements in these measures, but that of the other two studies did not. Nevertheless, significant reductions in total cholesterol and LDL-cholesterol (p<0.01 and <0.05, respectively), and borderline significant improvements in BMI and heart rate (p=0.07 and p=0.08, respectively), were seen in study 3.

Correlative analyses: As shown in table 3, significant positive associations between physical activity levels and expression of CD36 or ABCA1, and significant negative associations between physical activity levels and MMP-9 expression, systolic BP or diastolic BP, or arterial stiffness, were observed. ABCA1 expression correlated inversely with fasting plasma glucose, while MMP-9 expression correlated with systemic vascular haemodynamic measures (including systolic BP and AIX) and systemic measures of CVD risk (including fasting plasma levels of total and LDL-cholesterol). Therefore, the current data appear to support our previous proposals that exercise-triggered cell signalling events which can be detected in monocytes may contribute to mechanisms that underpin systemic CVD risk-lowering health benefits.

DISCUSSION

Relevance to practice: The major conclusion of this investigation is that cardiovascular health benefits in line with those seen in our previous investigations were observed—albeit to slightly differing extents—in all three studies. Study 1 participants underwent significant decreases in anthropometric measures such as BMI and waist circumference, in vascular haemodynamic measures such as BP, and in clinical measures such as insulin sensitivity (see table 1). The majority of these effects were also seen in study 3 participants, and in members of the adherent group within study 2; also, arterial stiffness (which was not measured in study 1) underwent decreases in both study 2 (decreased AIX (see table 1))
Table 1  A comparison of ‘Δ-change’ (ie, week 8 vs week 0) measurements obtained from participants who completed three separate 8-week exercise programmes (**p<0.01; *p<0.05; (*)p<0.10, as detected via paired (ie, weeks 8 vs 0) t tests in each case)

| Study 1 (n=22) | Study 2 (n=65) | Study 3 (n=11) |
|---------------|---------------|---------------|
| **Physical activity** | **Adherent gp; n=32** | **Non-adherent gp; n=33** |
| Number of additional steps/week | 30 000 | 8684±236*** | NA |
| Number of/duration of sessions/week | 3×45 min | 2×34±3 min | NA |
| METs per session | 4.74 (or 14.22/week) | 3.58±0.06 (or 7.16/week) | NA |
| Δ IPAQ MET-min/week | 540±0 | 296±29** | −51±37 |
| **Anthropometric** | | | |
| Δ Mass (kg) | −0.9±0.3*** | 0.2±1.3 | 0±1.1 |
| Δ BMI (kg/m²) | −0.4±0.1** | 0±0.6 | −0.3±0.4 |
| Δ Waist circumference (cm) | −5.5±1.1*** | −0.8±2.6 | −0.8±1.9 |
| **Biomolecular** | | | |
| Δ CD36 (cf. week 0) | 1.90±0.50* | 1.88±0.21* | 1.15±0.26 |
| Δ ABCA1 (cf. week 0) | 1.95±0.31* | 2.78±0.45* | 1.47±0.46 |
| Δ MMP-9 (cf. week 0) | 0.52±0.16** | 0.69±0.08*** | 1.14±0.10 |
| **Vascular haemodynamic** | | | |
| Δ Systolic BP (mm Hg) | −6.1±2.6* | −6.0±9.0** | −1.0±5.0 |
| Δ Diastolic BP (mm Hg) | −0.6±1.8 | −3.0±6.0** | 1.0±4.0 |
| Δ Pulse pressure (mm Hg) | −5.5±2.4* | −3.0±9.0 | −2.0±6.0 |
| Δ Mean arterial pressure (mm Hg) | −2.5±1.7(+) | −4.0±6.0** | 0±4.0 |
| Δ Central systolic BP (mm Hg) | (−) | −5.0±7.0** | 0±5.0 |
| Δ Central diastolic BP (mm Hg) | (−) | −3.0±7.0** | 2.0±3.0 |
| Δ Central pulse pressure (mm Hg) | (−) | −2.0±7.0 | −1.0±5.0 |
| Δ Alx at HR 75 bpm (%) | (−) | −4.0±6.0** | 1.0±7.0 |
| Δ MAP-adjusted carotid-femoral PWV (m/s) | (−) | 0.1±0.4 | 0.1±0.4 |
| Δ HR (bpm) | −2.2±2.9 | −1.0±8.0 | 2.0±9.0 |
| **Clinical** | | | |
| Δ Triglycerides (mmol/L) | 0.1±0.1 | −0.1±0.4 | −0.2±0.6 |
| Δ Total cholesterol (mmol/L) | 0.3±0.4 | −0.1±0.5 | 0.1±0.4 |
| Δ HDL-cholesterol (mmol/L) | 0.1±0.1 | 0.1±0.3 | 0±0.3 |
| Δ LDL-cholesterol (mmol/L) | −0.1±0.2 | −0.1±0.9 | 0.1±0.5 |
| Δ Glucose (mmol/L) | −0.1±0.1 | 0.1±0.5 | 0±0.2 |
| Δ Insulin (pmol/L) | −16.2±9.6(+) | −0.2±4.1 | 0.3±4.6 |
| Δ HOMA-IR (mmol/L, μU/mL) | −0.6±0.3* | 0±0.1 | 0±0.1 |

ABCA1, ATP-Binding Cassette protein A1; Alx, Augmentation Index; BMI, body mass index; BP, blood pressure; CD36, cluster of differentiation isoform-36; HDL, high-density lipoprotein; HOMA, homoeostatic model assessment; HR, heart rate; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; MAP, mean arterial pressure; MMP-9, matrix metalloproteinase-9; NA, not available; PWV, pulse wave velocity.
and study 3 (decreased PWV (see table 1); this discrepancy may be because study 3 participants were older, as aPWV rather than AIX has been reported to be a more sensitive measure of arterial stiffness in individuals of age >55 years\(^3\)). Interestingly, parameters for which studies 2 and 3 did not achieve significance included body mass and waist circumference; this ability of studies 2 and 3 to achieve CVD risk-lowering benefits without impacting on body mass/waist circumference may be of interest in itself, due to the widespread focus on weight loss as a motivating factor with regard to promoting engagement in physical activity initiatives.\(^3\)

It should be noted that study 1 involved continuously monitored sessions that took place under the constant supervision of researchers. While this was possible within a university setting, such an approach is not feasible in community-based or exercise-referral programmes. Importantly, studies 2 and 3 were undertaken on a one-leader-per-group-of-participants basis, an approach which has been reported to be suitable for increasing patient engagement in physical activity initiatives.\(^2\)

The current study obtained data that can enhance self-determination for exercise has been highlighted.\(^3\) Importantly, the current study obtained data that can address this deficiency, in that study 2’s adherent group underwent numerous improvements in CVD risk-related measures (see table 1) that were not seen in the non-adherent group. Although exercise-referral specialists use motivational interviewing techniques to attempt to foster self-regulatory behaviour, patients who are attempting to exert self-control in other aspects of their lives may suffer resource depletion, which ultimately will affect adherence.\(^3\) This has been identified as a factor that may impact unfavourably on adherence to NERS programmes,\(^1\) and the need for additional strategies to enhance self-determination for exercise has been highlighted.\(^3\) The current study’s demonstration of adherence-associated differences in impact suggest that

| Table 2 Baseline data from participants in three separate 8-week exercise programmes (***p<0.001; **p<0.01; *p<0.05; \(^(*)p<0.10\), as detected via one-way ANOVA with Tukey’s post hoc analysis in each case) |
|-------------------------------|----------------|----------------|----------------|
| Anthropometric                | Study 1 (n=28) | Study 2 (n=65) | Study 3 (n=14) |
| Mass (kg)                     | 78.2±13.4     | 75.8±2.2       | 86.6±6.2       |
| BMI (kg/m\(^2\))              | 30.0±5.0      | 28.7±0.7       | 30.8±1.6       |
| Waist circumference (cm)      | 93.4±14.0     | 87.1±1.8       | 101.9±4.7**    |
| Age (years)                   | 44.6±2.4      | 44.5±1.7       | 56.0±3.9**     |
| Vascular haemodynamic         |               |               |               |
| Systolic BP (mm Hg)           | 129.2±12.5    | 126.6±1.8      | 126.7±3.3      |
| Diastolic BP (mm Hg)          | 78.1±8.8*     | 84.8±1.3       | 85.4±3.7       |
| Pulse pressure (mm Hg)        | 47.4±2.0**    | 41.8±1.1       | 42.2±2.7       |
| Mean arterial pressure (mm Hg)| 95.2±7.8      | 98.7±11.3      | 99.6±8.7       |
| Central systolic BP (mm Hg)   | (−)           | 112.9±1.6      | 116.7±4.2      |
| Central diastolic BP (mm Hg)  | (−)           | 78.3±1.3       | 85.6±3.9*      |
| Central pulse pressure (mm Hg)| (−)           | 34.5±1.4       | 28.9±2.2*      |
| AIX at HR 75 bpm (%)          | (−)           | 20.0±1.5       | 32.3±3.2(*)    |
| MAP-adjusted carotid-femoral PWV (m/s) | (−) | 6.95±0.2 | 8.22±0.5*   |
| HR (bpm)                      | 80.0±11.4     | 66.2±1.3*      | 74.4±4.1       |
| Triglycerides (mmol/L)        | 1.4±0.1       | 1.0±0.1        | 1.4±0.1        |
| Total cholesterol (mmol/L)    | 4.9±0.2       | 4.8±0.1        | 6.4±0.4**      |
| HDL-cholesterol (mmol/L)      | 1.5±0.1       | 1.6±0.1        | 1.4±0.1        |
| LDL-cholesterol (mmol/L)      | 2.8±0.2       | 2.8±0.1        | 4.4±0.3**      |
| Glucose (mmol/L)              | 4.8±0.1       | 4.8±0.1        | 5.8±0.4***     |
| Insulin (μmol/L)              | 52.4±12.0     | 31.0±15.5      | 52.2±10.7      |
| HOMA-IR (mmol/L.μU/mL)        | 1.7±0.4       | 1.0±0.1        | 1.0±0.3        |

ANOVA, analysis of variance; AIX, Augmentation Index; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA, homoeostatic model assessment; HR, heart rate; LDL, low-density lipoprotein; MAP, mean arterial pressure; PWV, pulse wave velocity.
Table 3  Selected associations between physical activity (ie, participation in the 8-week exercise programmes described in the text) and biomolecular, vascular haemodynamic, and clinical parameters related to CVD risk (see text for details).

| Parameter                      | r        | p Value |
|--------------------------------|----------|---------|
| **Physical activity**          |          |         |
| IPAQ (MET-min/week)            |          |         |
| **Biomolecular**               |          |         |
| MMP-9 expression               | -0.502   | <0.001  |
| CD36 expression                | 0.343    | 0.013   |
| ABCA1 expression               | 0.356    | 0.010   |
| **Vascular haemodynamic**      |          |         |
| Systolic BP (mm Hg)            | -0.371   | 0.004   |
| Diastolic BP (mm Hg)           | -0.475   | <0.001  |
| Mean arterial pressure (mm Hg) | -0.459   | <0.001  |
| Central systolic BP (mm Hg)    | -0.323   | 0.013   |
| Central diastolic BP (mm Hg)   | -0.327   | 0.011   |
| Alx at HR 75 bpm (%)           | 0.293    | 0.029   |
| MAP-adjusted carotid-femoral   | -0.340   | 0.015   |
| PWV (m/s)                      |          |         |
| **Biomolecular**               |          |         |
| MMP-9 expression               | 0.420    | 0.014   |
| **Vascular haemodynamic**      |          |         |
| Systolic BP (mm Hg)            | 0.354    | 0.003   |
| Pulse pressure (mm Hg)         | 0.282    | 0.050   |
| Alx at HR 75 bpm (%)           | 0.398    | 0.015   |
| Total cholesterol (mmol/L)     | 0.363    | 0.027   |
| LDL-cholesterol (mmol/L)       |          |         |
| ABCA1 expression               |          |         |
| Glucose (mmol/L)               | -0.329   | 0.028   |

Bivariate correlation analyses were carried out using Pearson’s method, with ‘Δ changes’ (ie, differences between measurements taken pre-exercise at weeks 0 and 8 of the intervention) as the source data for these analyses. (Please note that parameters that did not exhibit significant correlations were omitted from this table.) ABCA1, ATP-Binding Cassette protein A1; Alx, Augmentation Index; BP, blood pressure; CVD, cardiovascular disease; HR, heart rate; LDL, low-density lipoprotein; MAP, mean arterial pressure; MMP-9, matrix metalloproteinase-9; PWV, pulse wave velocity.

CONCLUSIONS

The current manuscript presents evidence that the majority of the exercise-associated effects on both biomarkers and measurable health benefits reported in our previous laboratory-based studies5 6 8–12 are also observed in participants exercising in community-based and exercise-referral settings. Also, the CVD risk-lowering benefits seen in NERS participants with overt CVD-related conditions were similar to those seen in healthy cohorts (see studies 2 and 3, and our previous studies5–14). These findings may be of use in guiding policymakers with regard to the introduction and/or continued implementation of community-based and clinically associated exercise-referral programmes.

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provision of biomarker feedback data to exercise-referral patients may be of use in improving participants’ motivation to adhere to their recommended exercise programmes.

Limitations The research described in the current manuscript has several limitations. First, the cohort sizes are relatively small. Second, the studies were run on a within-group basis, with baseline values (rather than a separate control cohort) acting as comparators, rather than the randomised control trial format used in previous NERS evaluations.18–21 However, our approach is congruent with current National Institute for Health and Care Excellence (NICE) guidelines36 and the NHS Standard Evaluation Framework for physical activity interventions,37 which cite investigation of whether primary and secondary outcomes have changed over the course of the intervention as appropriate practice. Finally, while the three studies are broadly similar in design and aims, they are not identical (eg, more involved haemodynamic measurements such as Alx and aPWV were not carried out in study 1). Nevertheless, despite these acknowledged limitations, we hope that the current manuscript is seen as making a valid contribution to the ongoing debate with regard to implementation of exercise in clinical and public health settings.18 20–23 34
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