Brunel University

School of Health Sciences and Social Care

Doctor of Philosophy Thesis

The EPAF-Study

The EUROACTION Physical Activity and Fitness Study

A paired, cluster-randomised controlled trial in 8 European countries in people with coronary heart disease and individuals at high risk of developing cardiovascular disease

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I declare that this is original work and an account of my own research

Dedicated to:

My 11-year old daughter Ella for her patience and much understanding for all the time we've had apart to achieve this ambition.

The captain, shipmates and crew of the "good ship EUROACTION" for a truly remarkable journey of academic and personal growth.

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Abstract

Context: Increased physical activity participation and fitness are cardioprotective. The EUROACTION trial demonstrated that a preventive cardiology programme significantly increased self-reported physical activity participation (Wood et al., 2008). ***Objective:*** The EUROACTION Physical Activity and Fitness (EPAF) Study aimed to objectively evaluate the effectiveness of the EUROACTION physical activity and exercise intervention at increasing physical activity participation and fitness in people with coronary artery disease (COR) and those at high risk of developing cardiovascular disease (HRI) compared to standard care. ***Study design:*** A nested study within a paired cluster randomised controlled trial in eight European countries. ***Methodology:*** 12 pairs of centres (12 hospitals and 12 general practices) were randomised to receive the EUROACTION programme (INT) or be monitored for usual care (UC). In the INT hospitals, COR patients participated in a 16-week supervised exercise programme and a home-based activity intervention, delivered by a physiotherapist. In INT general practice nurses were trained to deliver personalised physical activity advice to HRI. ***Outcome measures:*** Objective physical activity participation was measured by mean number of steps per day (Yamax Digiwalker SW200 pedometer). Fitness was determined by the Incremental Shuttle Walk Test (ISWT) [hospital centres] and Chester Step Test (CST) [general practice centres]). ***Results:*** The mean number of steps in COR patients at 1–year was significantly higher in INT (+2310 steps, 95% CI +1226 to +3394 steps; P=0.003). The difference in cardiorespiratory fitness (ISWT) exceeded the minimal clinically important difference but was not statistically significant (+54 metres [95% CI -102.8 to +211.0 metres]; P=0.42). In general practice centres, whilst no significant differences were found at 1 year in mean steps per day (+982 steps, 95% CI -569 to +2533 steps) and cardiorespiratory fitness (CST) at 1-year (+0.93 minutes, 95% CI -0.62 to +2.48 minutes), there was a difference in the change over time in fitness in favour of the INT (+0.94 mins [95% CI +0.23 to +1.66 mins]; P=0.02). Marked heterogeneity impacted on statistical power. All differences observed represented clinically important differences. ***Conclusion:*** The EPAF-Study has demonstrated that the EUROACTION programme was effective at increasing physical activity participation but objective measures indicate to a lesser degree than the self-reported physical activity outcomes previously published. Clinically important differences in objectively measured physical activity participation and cardiorespiratory fitness suggest further research, which is sufficiently powered, is warranted.

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List of Abbreviations and Acronyms

BHF	British Heart Foundation
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
COR	Coronary patients
CR	Cardiac Rehabilitation
CRF	Cardio Respiratory Fitness
CST	Chester Step Test
CVD	Cardiovascular Disease
DALY's	Disability-Adjusted Life Years
DLW	Doubly Labelled Water
EGPA	European Guidelines for Physical Activity
EOP	End of Programme Assessment
EPAF	EUROACTION Physical Activity and Fitness
FITT	Frequency, Intensity, Time & Type
HDL	High Density Lipoprotein
HRI	High Risk Individuals
HR	Heart Rate
HRmax	Heart Rate Maximum
HRR	Heart Rate Reserve
IA	Initial Assessment
IHD	Ischaemic Heart Disease
IHF	Irish Heart Foundation
INT	Intervention
ISWT	Incremental Shuttle Walk Test
LDL	Low density lipoprotein
METs	Metabolic Equivalents of Tasks of Daily Living
MI	Myocardial Infarction
NACR	National Audit of Cardiac Rehabilitation
NCDs	Noncommunicable Diseases
NGOs	Nongovernmental Organisations
NICE	National Institute of Health and Clinical Excellence
PRNS	Partners and significant others
RCT	Randomised Controlled Trial
RPE	Rating of Perceived Exertion
SCD	Sudden Cardiac Death
6-MWT	Six Minute Walk Test
7-DAR	7-Day Activity Recall
TC	Total Cholesterol
UC	Usual Care
UC-SS	Usual Care Sub-Sample
UK	United Kingdom
UN	United Nations
VO_2	Oxygen Uptake
VO_{2max}	Maximal Oxygen Uptake
WHF	World Heart Federation
WHO	World Health Organisation

Thesis Foreword

The context of this study, and my specific contribution, is important in introducing this thesis. The EUROACTION programme was born in recognition of the EUROASPIRE survey findings which identified an unacceptable gap in the implementation of prevention guidelines into daily clinical practice (Kotseva et al., 2009a; 2009b). National coordinators from the 24 countries participating in EUROASPIRE were invited to collaborate in a grant application to the European Society of Cardiology (ESC) for a research programme which set out to demonstrate if a structured preventive cardiology programme could better help patients with coronary heart disease, high multifactorial risk, and diabetes to effectively achieve the lifestyle, risk factor, and therapeutic targets defined in the ESC guidelines.

The principle applicant, Professor David Wood, was the clinical lead for a preventive cardiology programme at Charing Cross Hospital, London. The programme comprised (and still does) of a nurse-led multi-disciplinary team approach, coupled with the support of a patient's partner and family. It is considered exemplary in the United Kingdom; winning one of the top three programmes in the "British Heart Foundation Celebrating Cardiac Rehabilitation Award" in 2011. The basis of the grant application was to evaluate this type of model, compared to current practice, across other centres in Europe.

Eight national coordinators originating from the EUROASPIRE study group, including the United Kingdom (UK), enrolled as listed collaborators. The countries included in the study were consequently opportunistic. Following a successful application to the ESC for €1.3 million (originating from an unconditional education grant from AstraZeneca), a steering group was formed comprising of each National Coordinator (and later a principle investigator from each locality) together with the "Central Coordinating Team", the Statistical Centre (Ghent University, Belgium) and Health Economics Team (Brunel University, UK).

Funding was included within the programme grant for a nurse, dietetic and physiotherapy lead to join the "Central Coordinating Team". I was successful in my application and seconded from Brunel University on a part-time basis as the "Physical Activity Lead". Each of us were given responsibility to lead the design, development and implementation of specific components of this demonstration programme in preventive cardiology (Table a).

Table a: Key Areas of Responsibility by Profession

Profession	Key responsibilities
Physiotherapy lead	• Contribute to the overall study design in conjunction with the steering group. • Development of the physical activity and exercise components of the study including database design and validation. • Recruitment of EUROACTION physiotherapists for the hospital intervention groups. • Training of intervention and usual care teams in assessment of physical activity. • Train, oversee and quality assure the physical activity intervention in centres allocated to the EURACTION programme. • Manage the imputation, validation and analysis of the physical activity and exercise data.
Nurse lead	• Contribute to the overall study design in conjunction with the steering group. • Development of smoking cessation, medical risk factor assessment and psychosocial health components of the study including database design and validation. • Recruitment of EUROACTION intervention and usual care nurses • Training of intervention and usual care teams in assessment of smoking, medical risk factor management and psychosocial health status. • Oversee and quality-assure the smoking cessation intervention in centres allocated to the EURACTION programme. • Oversee and quality-assure the medical risk factor intervention in centres allocated to the EURACTION programme. • Oversee and quality-assure the psychosocial health intervention in centres allocated to the EURACTION programme. Manage the imputation, validation and analysis of smoking, medical risk factor and psychosocial health data.
Dietetic lead	• Contribute to the overall study design in conjunction with the steering group. • Development of the nutrition and weight management components of the study including database design and validation. • Recruitment of EUROACTION dietitians for the hospital intervention groups. • Training of intervention and usual care teams in assessment of nutritional intake and anthropometrics. • Oversee and quality-assure the nutrition and weight management intervention in centres allocated to the EURACTION programme. • Manage the imputation, validation and analysis of the diet and anthropometrics data.

The nurse lead, dietetic lead and I each registered for a Doctorate in Philosophy (PhD). In essence, the research settings and study population were a result of the collective steering group and were pre-defined. Whilst we each contributed to the collective decisions of the steering group, we recognised the need to design a "study within a study" that fell outside of the steering group's jurisdiction in order to be able to demonstrate our unique contributions. To emphasise, I was the only exercise professional on the steering group and therefore my contribution was unique in itself. I was given full responsibility in designing and implementing the physical activity intervention and therefore this part of the main study was very much my own work.

My nurse colleague, now Dr Catriona Jennings, evaluated the concordance for lifestyle change in families. She analysed the EUROACTION dataset to investigate the effectiveness of the EUROACTION programme in patients who came alone versus patients attending with a significant other – either from the same household or living elsewhere.

In relation to diet, the main EUROACTION study outcomes included achieving the ESC dietary recommendations for cardiovascular disease prevention using a food frequency questionnaire; essentially an interview-administered questionnaire of self-reported diet. For her PhD, the dietitian (now Dr Alison Mead) evaluated an inflammatory biomarker in a random sub-sample of the EUROACTION study population of coronary patients to evaluate the impact of the programme beyond self-reported measures.

My research question focussed on trying to more objectively evaluate the effect of the EUROACTION programme on physical activity participation and fitness. The primary outcome of the main study derived from the collective steering group was the achievement of the European Guidelines for Physical Activity (EGPA); based on the same self-reported measures used in the EUROASPIRE surveys, from which the EUROACTION study was born (i.e. this measure was essentially pre-defined). This in my view was a soft end point and I wanted to evaluate physical activity participation more objectively *and* as importantly the impact of the programme on physical fitness given the strong association between fitness and all-cause mortality.

Despite my recommendations to the steering group there was no funding available to measure physical activity and exercise beyond self-report and I consequently sought additional funding from AstraZeneca for accelerometers and fitness test equipment. The funding secured was not sufficient for accelerometers (unless I only included a very small sample) and therefore, after much research, I selected a particular model of pedometer as the alternative.

When reading this thesis it is important to be aware that the EUROACTION study was essentially 2 research programmes; where the research settings, intervention design and study populations were different. Both studies are presented within this thesis at the advice of my supervisor.

The first study was based in 12 hospital settings and included a study population of coronary patients and their families. The six intervention centres comprised of a multidisciplinary team delivering a once-weekly 16-week programme which aimed to achieve the lifestyle, risk factor, and therapeutic targets defined in the ESC guidelines. The remaining six hospital centres were monitored for usual care.

The second study started 15-months later and was based in 12 general practice centres. Here the study population were people who were asymptomatic, with no known cardiovascular disease but found to be at high risk of developing disease, together with their families. In this second study the intervention was designed very differently to that being delivered in the hospital setting. In the six general practices assigned to the intervention, a nurse delivered a protocol driven 1-year intervention, which akin to the hospital study aimed to achieve the lifestyle, risk factor, and therapeutic targets defined in the ESC guidelines. The remaining six general practice centres were monitored for usual care. Given the time lag between the 2 studies, I had the opportunity with the second study to incorporate my learning and improve my study design.

Investigating the effects of the programme more objectively was important. There were unique aspects to the programme that could have considerable consequences for future health care delivery. For example, in relation to the first study, national guidelines in the United Kingdom (UK) at the time supported twice weekly supervised cardiac rehabilitation to people affected by heart attack or following revascularisation (SIGN, 2002; BACR 1995).

The EUROACTION programme used a once weekly approach in its coronary population (due to limitations in funding essentially) and consequently if found to be effective could suggest a cost-saving model of care for the National Health System (NHS).

I also designed an exercise intervention purposefully using minimal equipment that could be delivered in a wide array of settings. The main reason I did this was in recognisition of the need to create a model that could be replicated at home; especially as I was very aware that the programme for the coronary patients and their families was being delivered once weekly. In the knowledge that less than half of coronary patients avail of a cardiac rehabilitation programme (both in the UK and across Europe), I also incorporated invitation letters that specifically used cognitive and motivational techniques in an attempt to increase uptake. On starting the programme, I also included a "contract" with each participant in light of evidence suggesting this may result in improved completion rates.

Hence if these low-cost approaches were demonstrated to be effective this has important implications for informing service delivery both nationally and across Europe as a whole. Finding an effective model that is not dependent on equipment increases the feasibility of the intervention to be delivered in a wider range of venues and motivational letters and contracts with the participants are very simple measures that could realistically be applied to every cardiac rehabilitation programme if found to be effective.

Similarly in the second study in primary care, general practice nurses were trained to deliver a specific protocol driven physical activity intervention, designed by the author in response to a review of effective strategies to raise physical activity participation. Given that 2 in 3 older adults are not achieving the physical activity recommendations in the United Kingdom, nor across Europe as a whole, there is enormous scope to improve health if this practice nurse intervention was found to be effective (BHF, 2012a; European Commission, 2014). Using self-report as the only measure would not provide strong enough evidence, given the tendency to over-report activity, and therefore incorporating objective measures to investigate the effect of practice nurses at increasing activity levels and fitness was in my view of critical importance.

To select the additional measures to determine physical activity participation and fitness, in addition to a detailed literature review, I sought the advice and opinions from colleagues in the British Heart Foundation Research Group (in particular Professor Charlie Foster) and experts in physical activity research (in particular Professor Marie Murphy, Professor Nanette Mutrie and Professor Fiona Bull). Once I had my measures determined, I worked closely with the database design team in the development of the physical activity and exercise fields. This included incorporating data validation and generating data queries as part of audit and quality control.

I also felt strongly that it was essential to employ health professionals with the required knowledge, skills and competences to deliver the EUROACTION programme. This required working with the Principle Investigator from each centre and supplying detailed job descriptions, writing advertisements for the posts and short listing candidates for each of the centres. I personally interviewed all candidates (with the help of translators) and recruited the people I assessed as strongest to deliver the EUROACTION intervention. I also then trained this pan-European team; designing and delivering my own training programme. The training was accompanied by a "Health Professional Manual" to which I was the sole contributor in relation to the physical activity and exercise component.

To provide clarity regarding my role in relation to data imputation, validation and analyses: my team of physiotherapists, practice nurses and usual care nurses were trained by me to enter the data using the EUROACTION database. I requested monthly audit reports from the central data management team in order to monitor for recruitment and communicated missing data reports to the team. I worked with the statistical centre in Ghent with regards to the analyses for the primary end point and then for my analyses relating to this PhD, I carried out these analyses myself (after completing a 2-week intensive course in medical statistics and being trained to use STATA statistical software). However, in order to ensure I had used the exact same random effects modelling, all my statistical analyses were also carried out and verified by the Central Statistical Centre.

In closing, my research journey with the EUROACTION trial has resulted in immense learning and personal growth. I've learnt that research is all about thinking, thinking and thinking again. With the time delay between the two parts to the study I had the opportunity to try to improve on my research design and still I'm left thinking again. I've learnt so much academically from invaluable exposure to experts in epidemiology, medical statistics and the subject area of preventive medicine. On a personal level, I have had the opportunity to broaden my horizons. Direct exposure to different cultures, healthcare structures and environments across 7 different countries to my own has changed the way I think and broadened my horizons.

With receiving major corrections, I've had to think again and better understand my research question. This research journey has made me recognise a need to grow in self-confidence as this affects our performance and success in all walks of life, from sports to socialising to dating. It plays a role in research too. Overcoming a fear of failure has been an important achievement. The failures have increased my understanding, maturity and ability to problem-solve.

In conclusion, this foreword introduces you to the context of this thesis. EUROACTION was a large study (with a hospital study and a general practice study) and I was part of a team managing this largest demonstration programme of its kind in Europe. The centres recruited to the study, the study population and the sample size were all pre-defined and consequently this Doctorate study should be viewed as "a study within an existing study". To emphasise my unique contribution, I was the only exercise professional within the steering group and as a result completely led the design and implementation of the physical activity and exercise intervention. My PhD study, entitled the EUROACTION Physical Activity and Fitness Study (EPAF-Study), aimed to investigate whether the intervention was effective in raising activity levels and physical fitness using objective measures with the purpose being to answer the research question in a more scientifically rigorous way. The scientific evidence for the role of physical activity and exercise in cardiovascular disease prevention is compelling and yet the prevalence of inactivity continues to be of major concern. If this intervention was found to be effective there is a real opportunity to transform the design, delivery and outcome of cardiovascular prevention and rehabilitation as part of a much needed solution for the growing burden of cardiovascular disease in Europe.

Chapter 1: Introduction

Despite declining trends in developed countries, cardiovascular disease (CVD) remains the leading cause of death worldwide (WHO, 2011). More than 17 million people died from CVDs in 2008. More than 3 million of these deaths occurred before the age of 60. In Europe, CVD remains the main cause of death accounting for 48% of all deaths, which equates to over 4.3 million deaths each year (European Heart Network, 2011). The same can be seen in the United Kingdom (UK) where coronary heart disease (CHD) is the most common cause of premature death and a leading cause of disability; accounting for 80,000 deaths in the UK in 2010, i.e one in five men and one in eight women (British Heart Foundation, 2012).

Whilst the past three decades have seen a reduction in the number of deaths overall from CVD in Europe there is a growing population of people surviving and living longer with these chronic long-term conditions. Moreover, negative trends in diabetes and obesity levels support the clear need to prioritise preventive care. The INTERHEART study provides convincing evidence that CVD is preventable by lifestyle changes (Yusuf et al., 2004). Based on the findings of this large international case-controlled study, it appears that almost 90% of heart disease is caused by nine potentially modifiable risk factors. Through regular physical activity, eating a healthier diet and by not smoking, it is possible to profoundly reduce the risk of myocardial infarction in both sexes and all age groups. Contrary to what was previously believed, heredity or the genetic makeup of a person does not play a major role in causing CVD (Buttar et al., 2005).

The need to address the global burden of CVD was evidenced by the "High-Level Meeting of the United Nations" on Non-Communicable Disease Prevention and Control in September 2011, in New York. This was the second time only that the group had ever been called upon in relation to a health issue; the first meeting was in relation to Human Immunodeficiency Virus. This in itself speaks volumes. The United Nations and World Health Organisation (WHO) have committed to reducing mortality from non-communicable diseases by a quarter between 2015 to 2025 (the 25 by 25 declaration) (Horton, 2013).

A wealth of epidemiological evidence supports the role of both *physical activity* and *physical fitness* in the prevention and control of cardiovascular disease. Findings from several randomised controlled trials (RCT's) suggest mechanisms for the cardioprotective nature of exercise training (Slentz et al., 2007; Rauramaa et al., 2004; Kraus et al., 2002). In secondary prevention, over 40 RCT's provide evidence for the health benefits of exercise-based cardiac rehabilitation (Heran et al., 2011; Taylor et al., 2004). It is therefore entirely justified for the "25 by 25 declaration" to include increasing activity levels globally as a means to achieve reducing the burden of non-communicable diseases; setting a target for every country in the World to achieve a ten per cent reduction in physical inactivity over a ten year period.

According to the World Health Report 2000, physical inactivity was estimated to cause 1.9 million deaths worldwide every year (WHO, 2000). The burden of illness and disease related to physical inactivity costs society a great deal in terms of increased healthcare costs and production losses. The European Union Public Health Information System (EUPhix) estimates that physical inactivity might cost a country about EUR 150–300 per citizen and year (European Commission, 2006). Given that physical activity has both health promoting and disease prevention properties, an increase in physical activity is one of the measures that would have the greatest positive impact on the health of the population.

The European Action on Secondary and Primary prevention through Intervention to Reduce Events (EUROASPIRE) surveys showed that CVD prevention in routine clinical practice has remained inadequate over the past decade (Kotseva et al., 2010; Kotseva et al., 2009a; Kotseva et al., 2009b; EUROASPIRE II Study Group, 2001a; EUROASPIRE II Study Group, 2001b; EUROASPIRE Study Group, 1997). Longitudinally, the EUROASPIRE surveys demonstrate no improvements in physical activity participation; with only 30% of adults achieving the physical activity target. Whilst evidence-based guidelines exist translating this evidence into effective patient care is failing resulting in a need to invest in strategies that measurably improve outcomes for people with, or at risk of, cardiovascular disease.

In response to the EUROASPIRE survey findings, a research programme entitled "EUROACTION" was born. EUROACTION remains the largest European demonstration project in preventive cardiology to date. This multi-centre cluster randomised trial set out to investigate if the Fourth Joint Task Force of the European Society of Cardiology CVD Prevention Guidelines (Graham et al., 2007) could be more effectively implemented in every day clinical practice. The study methodology was published in the *European Heart Journal* (Wood et al., 2004) (Appendix 1) and the study findings were published in the *Lancet* (Wood et al., 2008) (Appendix 2). In brief, this nurse coordinated, multidisciplinary, family-based, ambulatory programme achieved healthier lifestyle changes and improvements in other risk factors for patients with coronary heart disease and those at high risk of cardiovascular disease and their partners than those in usual care. The study concluded that to achieve the potential for cardiovascular prevention, we need local preventive cardiology programmes adapted to individual countries, which are accessible by all hospitals and general practices caring for coronary and high-risk patients.

In my capacity as the lead for physical activity, I contributed to both of the above publications and a number of scientific abstracts (Appendix 3). For the EUROACTION trial the primary outcome in relation to physical activity was the achievement of the European Guidelines for Physical Activity (EGPA) defined in the Fourth Joint Task Force CVD Prevention Guidelines (Graham et al., 2007). This outcome was based on the same self-reported measures used in the EUROASPIRE surveys. This PhD research, entitled the EUROACTION Physical Activity and Fitness Study (EPAF-Study), is a study within the EUROACTION trial that aims to evaluate the EUROACTION model beyond the achievement of guidelines. There are two parts to the study; a hospital-based study and a general practice study.

As the literature review reveals, there is a strong association between: a. increased physical activity participation and reduced all-cause mortality; and b. increased fitness and reduced all-cause mortality. Whilst there is a clear correlation, increasing physical activity does not necessary increase physical fitness. The activity performed has to be of the right dose and intensity to result in a positive impact on fitness. Consequently, in this study there are two primary outcomes; physical activity participation and physical fitness. The former was evaluated using a motion sensor to report mean steps per day, and the latter (physical fitness)

using sub-maximal exercise testing (the Incremental Shuttle Walk Test [ISWT] in the hospital study and the Chester Step Test [CST] in the general practice study).

This thesis aims to provide the rationale for including physical activity and physical fitness as primary outcomes, the justification for the choice of measurement tools and the underlying principles in the design of the EUROACTION physical activity intervention. The Lancet publication (Wood et al., 2008) demonstrates that the EUROACTION programme was effective in increasing the proportion of patients and their partners meeting the European guidelines for physical activity. The findings of the trial call for preventive cardiology programmes to be implemented by all hospitals and general practices caring for coronary and high-risk patients. To base a recommendation associated with this magnitude of investment on a single self-reported measure is inadequate. The EPAF-Study offers a more rigorous evaluation, using objective measures; providing an important contribution to informing the future design, delivery and outcome of cardiovascular prevention and rehabilitation as part of a much needed solution for the growing burden of cardiovascular disease in Europe.

Chapter 2:

Literature review

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2.3: *Changes in physical activity and fitness and mortality*

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2.7: *Interventions to increase participation in centre-based exercise programmes*

2.8: *Why include partners in the exercise intervention?*

2.9: *Closing remarks*

Cardiovascular disease (CVD) remains the single most common cause of death and disability in Europe; accounting for 47% of all deaths in Europe and 40% in the European Union (EU) (European Heart Network, 2012). Importantly, even though the EU is experiencing declining rates of mortality from cardiovascular disease, an increasing number of men and women are now living with cardiovascular disease. This paradox relates to increasing longevity and improved survival of people suffering from cardiovascular disease.

Overall CVD is estimated to cost the EU economy almost €196 billion a year (European Heart Network, 2012). Both population wide measures and improved access to individual health care interventions are required to reduce this major health and socioeconomic burden. Physical activity has an important role in many aspects of health, including most of the major non-communicable diseases which make the largest contribution to ill health worldwide (WHO, 2010). Recent estimates have suggested that physical inactivity may be responsible for up to 9% of all premature mortality worldwide and causes 6% of the total burden of disease from coronary heart disease (Lee et al., 2012). Given that physical inactivity is the fourth leading risk factor for mortality (World Health Organisation, 2009), interventions designed to increase activity levels should be fundamental to contemporary preventive cardiology practice.

The following chapter aims to firstly set the scene by describing the prevalence of cardiovascular disease and physical activity status in the eight countries included in the EUROACTION study. Following this description, this chapter will secondly explore the relationships between physical activity, exercise, physical fitness and CVD. The underlying cardioprotective mechanisms associated with regular physical activity will be considered. The third theme surrounds measurement of physical activity and fitness. Fourth and finally, irrespective of the benefits, it is important to recognise that a very high proportion of the population remain sedentary and so translating science into real world practice poses many challenges. This applies to secondary prevention too where highly effective interventions such as cardiac rehabilitation have little take-up. As a result, this chapter also gives appropriate recognition to evidence-based behaviour change strategies and interventions that are known to effectively improve uptake and adherence as well as increase physical activity participation and fitness.

2.1: Prevalence of CVD and physical activity statistics in Europe

CVD remains the main cause of death in Europe with very significant differences in mortality rates between countries. The differences are greatest between Northern, Southern and Western European countries and Central and Eastern European Countries. There are also differences between Western and Southern European countries with Southern European countries still having lower death rates from CVD than Western European countries (European Heart Network, 2012). Eight countries were included in the EUROACTION trial and their selection was entirely opportunistic. According to the latest statistics these countries all presented with lower than average mortality rates from CVD; ranging from 25% (France) to 41% (Sweden) of all deaths (Table 2.1.1).

Table 2.1.1: Total number of CVD deaths per year *(ranked lowest to highest)* (European Heart Network, 2012)

	Coronary Heart Disease n (% of all deaths)	**Stroke** n (% of all deaths)	**Other CVD's** n (% of all deaths)	**All CVD deaths** n (% of all deaths)
France	21,525 (8%)	13,497 (5%)	33,256 (12%)	68,278 **(25%)**
Netherlands	6,004 (9%)	3,462 (5%)	8,809 (13%)	18,275 **(27%)**
Spain	20,320 (10%)	13,215 (7%)	21,279 (11%)	54,814 **(28%)**
Denmark	3,257 (12%)	1969 (7%)	2,915 (11%)	8,141 **(30%)**
UK	47,306 (17%)	19,171 (7%)	21,322 (8%)	87,799 **(32%)**
Italy	38,176 (13%)	25,318 (9%)	35,158 (12%)	98,652 **(34%)**
Poland	25,407 (12%)	15,913 (8%)	42,293 (20%)	83,613 **(40%)**
Sweden	8,204 (19%)	3,111 (7%)	5,739 (13%)	17,054 **(41%)**
Average CVD mortality rate for Europe = 42% of all deaths				

The most recent multi-country data on physical activity among adults in Europe was the 2009 Eurobarometer survey on physical activity, which asked respondents to indicate how often they exercised or played sport and how often they participated in non-sport physical activities including active transport and incidental leisure time physical activity (European Commission, 2010). Participation in exercise or sport was relatively low across the EU, with 39% of adults overall reporting that they never participate in these activities and 21% participating three times per week or more (Table 2.1.2).

Whilst the mortality rate from CVD in each of the EUROACTION countries was below average, the frequency of exercising or playing sport more than three times a week was more variable, with Poland and Italy falling considerably short of the EU average. Despite Sweden having the highest mortality rate from CVD, it also has in this latest survey the highest rate of regular participation in exercise within the EURACTION countries (Table 2.1.2).

Table 2.1.2: Frequency of exercising or playing sport *(ranked by achieving a minimum of 3 times per week)* (European Commission, 2010)

	≥5 times per week (%)	**3 to 4 times per week (%)**	**1 to 2 times per week (%)**	**1 to 3 times per month (%)**	**Less often (%)**	**Never (%)**
Sweden	22	22	28	8	13	6
Denmark	15	18	31	7	11	18
UK	14	14	17	7	15	33
Spain	12	15	12	4	15	42
France	13	12	23	8	10	34
Netherlands	5	16	35	8	8	28
Poland	6	7	13	6	18	48
Italy	3	9	17	4	12	55
EU Average	**9**	**12**	**19**	**6**	**15**	**39**

Participation in less formal physical activity was also quite low across the EU. When asked „How often do you engage in a physical activity outside sport such as cycling or walking from a place to another, dancing, gardening…?", 14% of adults in the EU responded „Never" (Table 2.1.3). Those in Southern Europe tended to be less likely to participate in informal physical activity and more than a quarter of respondents in Italy reported never doing any physical activity. Informal physical activity was highest in the Netherlands, Demark and Sweden; these three were also ranked within the top across the EU as a whole.

Table 2.1.3: Frequency of participating in informal physical activity *(ranked by 5 or more times per week)* (European Commission, 2010)

	≥5 times per week (%)	**3 to 4 times per week (%)**	**1 to 2 times per week (%)**	**1 to 3 times per month (%)**	**Less often (%)**	**Never (%)**
Denmark	43	18	24	7	4	4
Netherlands	42	20	22	7	4	5
Sweden	40	21	23	7	7	2
UK	37	15	21	7	9	11
Spain	33	22	16	7	12	10
France	33	17	25	9	6	10
Poland	26	15	19	9	10	17
Italy	7	9	21	14	16	33
EU Average	**27**	**17**	**21**	**9**	**11**	**14**

In summary, whilst the countries included in the EUROACTION trial represent countries with a below average incidence of mortality from CVD in Europe, these illness remain at large. CVD continues to be the number one killer and cause of disability in all eight EUROACTION countries. Dramatic increases are being seen in the number of people surviving and living longer with these chronic long-term conditions. Moreover, one-third of Europeans have three or more risk factors and these risks are increasing as the population ages. This, together with negative trends in diabetes and obesity levels, supports the clear need to prioritise preventive care.

There is no doubt that across Europe (and globally) we are faced with a looming epidemic – the costs of treating CVD and loss of productivity are staggering. Increasing physical activity has one of the greatest positive impacts in reducing this burden; both in relation to healthcare utilisation and health economics. A review of studies in the United States has shown that for every one dollar invested into an effective prevention programme that increases physical activity, five dollars in health care costs are saved (Prevention Institute, 2007).

The latest statistics highlight there is enormous potential to capitalise on physical activity. In the EUROACTION countries less than half of adults (ranging from 7% to 44%) are regularly exercising or participating in adequate doses of informal physical activity. Identifying effective strategies to raise activity levels through quality research is of critical importance in saving lives, preventing disease and promoting recovery and well-being.

2.2: The evidence for physical activity, exercise and physical fitness in preventing premature death

The following aims to firstly define physical activity, exercise and physical fitness and consequently examine the evidence for their relationship with reduced risk of premature death together with the prevention of coronary heart disease, diabetes, obesity and the metabolic syndrome.

2.2.1: Epidemiology of physical activity, premature death and coronary heart disease

The terms physical activity, exercise and physical fitness are all intrinsically linked. Physical activity can be defined as any bodily movement produced by skeletal muscles resulting in energy expenditure. Exercise, on the other hand, is a sub set of physical activity, executed for a specific purpose, resulting in increased performance (Caspersen et al., 1985). Physical fitness (or commonly referred to as conditioning) can be considered a marker of an individual‟s ability to perform a given physical activity (Warburton et al., 2006). Conversely leading a sedentary lifestyle is associated with a reduction in physical fitness and a number of health-related conditions.

The benefits of physical activity have been known for centuries but it had taken a number of landmark epidemiological studies, dating from the 1950‟s, to confirm that it is cardioprotective. Bus conductors, postmen and active dockworkers were compared with their counterparts; bus drivers, telephonists and clerks respectively. The prevalence of mortality from myocardial infarction was approximately halved in those with more active occupations (Morris et al., 1990; Paffenbarger et al., 1978; Morris et al., 1953).

The earliest of these comparisons by Morris and colleagues (1953), involved a cross sectional evaluation of around 33,000 London transport workers comparing conductors, who climbed stairs 11 out of every 14 days for 50 weeks of the year, with bus-drivers. Morris found that the incidence of heart attack in the conductors was considerably lower than for bus drivers and even if they suffered a heart attack they were more likely to survive. However, Morris‟ work was heavily criticised given the numerous possible confounders, including self-selection with greater likelihood of less healthy employees taking up driver positions and increased stress levels in drivers compared to conductors.

Morris later to studied 9376 healthy male civil servants aged between 45-64 years at entry, following them for 9 years and 4 months. Of these, 474 men experienced coronary heart attacks (202 non-fatal, 272 fatal). The 9% of men who reported that they often participated in vigorous sports or did considerable amounts of cycling or rated the pace of their regular walking as fast (over 4.0 mph, 6.4 km/h) experienced less than half the non-fatal and fatal heart disease of the other men (Morris et al., 1990). The definition used for vigorous exercise involved peaks of energy expenditure of 7.5 kcal/min (31.5 kJ/min), >6 metabolic equivalents for tasks (METs), >65% of maximum oxygen uptake. In other words, for example walking at 4 miles per hour, an activity that today would be considered „moderate‟ in intensity, was classified as „vigorous‟. With this limitation of the classification of intensity in mind, people who participated in 2 sessions per week or more of vigorous sport had a third the risk of a myocardial infarction. So, for every 3 people having a heart attack 1 of these individuals participated in vigorous sport. A stronger correlation ($p<0.005$) was found between those undertaking vigorous sport and a lower incidence of cardiovascular events compared with those taking part in non-vigorous sport.

Further findings from this same study added weight to the suggestion that it is exercise intensity, as opposed to duration, that is the crucial factor in reducing coronary attack and death. Walking pace seemed to be a good predictor, with those who reported walking at 4 mph or faster presenting with a quarter of the risk compared to those who reported strolling; about a 4 fold difference. Conversely no relationship was observed between total walk duration, accumulated over the week, with coronary attack and death rate. This finding is however contrary to other more recent studies which support similar health benefits being associated with both continuous

and accumulated activity (Matthews et al., 2007; Smith et al., 2007; Gregg et al., 2003; Manson et al., 2002).

Morris et al., (1990) also investigated coronary attack (MI) and death in people who had previously participated in sports activity but had since given up and found no difference amongst these groups which suggests physical activity has to be recent to be protective. This is unsurprising given that coronary heart disease develops over years with a heart attack being an acute episode. Hence Morris‟ work highlights that physical activity helps to protect against the chronic but also the acute phase of coronary atherosclerosis.

Morris and colleagues (1990) found that in men, more vigorous exercise was associated with a reduced risk of heart attack. However, men taking regular physical activity were also found to have other healthy behaviours which may act as confounders. To counter this criticism Morris used multivariate analysis to screen out other possible reasons and found that the benefits of vigorous exercise were independent of stature, whether or not individuals were smokers, whether or not their parents were still alive or had died of CVD and whether they have a higher or lower body mass index. Combined findings from this study provide strong evidence that physical activity may provide some protection against coronary heart disease.

The protective effect of work-based activity was also demonstrated in San Francisco dockworkers (Paffenbarger & Hale, 1975). Six thousand, three hundred and fifty-one „longshoremen‟ were categorised according to measurements of their occupational oxygen uptake as „light‟ „moderate‟ or „heavy‟ work and followed up for 22 years. They found that men who engaged in light or moderate work were twice as likely to die from CHD as those whose work was classified as heavy. Selection bias was not as much of a concern as in the studies by Morris (cited above for bus conductors and drivers), as men enrolled to work on the docks were not allowed to choose their job assignment (Hardman & Stensel, 2009).

In the latter half of the twentieth century, attention switched to leisure-time physical activity and the findings of several cohort studies were published in the 1980‟s and 1990‟s. The most notable of these was the Harvard Alumni Health Study (Paffenbarger et al., 1986). This involved a cohort of men enrolled in Harvard College between 1916 to 1950. Participants completed questionnaires which were used to estimate the energy expended in walking, stair climbing, sports and leisure-based activities. Paffenbarger and colleagues assessed 16,936 men aged 35-74 years at baseline. Data was first collected in 1962 and 1966 and follow-up conducted 12-16 years later in 1978; by which time 1,431 alumni had died. An inverse dose-response relationship was found between energy expenditure and risk of all-cause mortality. Death rate was 25-33% lower amongst alumni who expended more than 2,000 kcal·week^{-1}.These findings remained significant even after controlling for smoking, blood pressure, body mass index and a positive family history for premature death. Further, there was evidence to suggest that very high levels of activity, defined as those achieving more than 3,499 kcal·week^{-1}, may be detrimental.

The age-adjusted relative risk of death in those expending between 2,500-2,999 kcal·week^{-1}, 3,000-3,499 kcal·week^{-1} and greater than 3,499 kcal·week^{-1} was 0.52, 0.46 and 0.62 respectively. However, the relative risk was still lower in the most active group compared to those expending less than 2,000 kcal·week^{-1}. Hence, findings from this study suggest, an optimal range of physical activity related energy expenditure of between 2,000 and 3,500 kcal·week^{-1} for health benefits.

Similar findings arise from more recent large cohort studies in women. The Women‟s Health Study, the Lipid Research Clinics Research Prevalence Study, and the Women Take Heart Project, reported an inverse and graded association between physical activity and mortality (Gregg et al, 2003; Gulati et al., 2003; Mora et al., 2003; Manson et al., 2002; Manson et al., 1999; Kushi et al., 1997). However, there is also the suggestion that „excessive‟ levels of activity may be detrimental. In one large prospective study, cardiovascular mortality was increased in the group of women reporting the highest levels of activity (Sherman et al., 1999), suggesting that the dose-response relationship appears to be curvilinear, with an „overdose‟ in the volume of physical activity being associated with increased adverse events.

There have been many other epidemiological studies since that time which have almost universally shown a positive effect. The Health Professionals Follow-up Study (Tanasescu et al., 2002) investigated 44,452 men from the United States of America, who were followed from 1986 to 1998. Physical activity was assessed every two years. This is an improvement on the previous methodology used by Morris et al., (2009) who measured physical activity via a questionnaire once for the 9.5 years of follow-up. Tanasescu et al. (2002) reported on the relative risk of CHD in men. They found that both increased exercise volume and intensity were protective. Moreover the same direct relationship was seen with running duration and weight lifting. Walking pace was associated with a significantly reduced relative risk of CHD; this relationship was not held for walking duration.

A major limitation of all of the studies reported above is their use of questionnaires to measure physical activity. Questionnaires are subject to error as they rely on accurate participant recall. A more recent study addressed this limitation by using the gold standard method of doubly labelled water tomeasure energy expenditure. In the Health, Ageing and Body Composition (Health ABC) study (Manini et al., 2006) energy expenditure was measured over a two-week period in 302 „high functioning" older adults aged 70-82 years. They were then followed up for just over 6 years on average. Death rates were two-thirds lower in the high physical activity group compared with the low physical activity group.

The Health ABC Study"s findings are noteworthy given they used a more objective measurement of physical activity. They found a 67% lower relative risk of death in the high activity group compared to the low activity group, which presents a stronger association than all the previous studies (above) which relied on questionnaires. In addition, this is similar to the strength of the association often observed between physical fitness and mortality thereby providing strong evidence that increased physical activity, and not just increased physical fitness, is cardioprotective.

The evidence for the benefits of physical activity is constantly growing and the *2008 United States Guidelines* (Physical Activity Guidelines Committee, 2008) cites 20 prospective cohort studies in physical activity and cardiovascular mortality published between 1995 and 2007. These are from many countries around the World including: the United States (7 studies) (Fang et al., 2003; Gregg et al., 2003; Manson et al., 2002; Rockhill et al., 2001; Sesso et al., 2000; Kushi et al., 1997; Kaplan et al., 1996); Finland(3) (Barengo et al., 2004; Hu et al., 2004; Haapanen et al., 1996); the United Kingdom (3) (Khaw et al., 2006; Yu et al., 2003; Wannamethee et al., 1998); Germany (2) (Raum et al., 2007; Mensink et al., 1996); Sweden (2) (Calling et al., 2006; Engstrom et al., 1999); Norway (1) (Wisloff et al., 2006); Canada (1) (Weller & Corey, 1998) and China (1) (Matthews et al., 2007). These studies included 68,000 men and 347,000 women in gender-specific analyses and 88,000 men and women in analyses that combined both genders. Since this review in 2008 there have been 4 additional prospective cohort studies published (Stamatakis et al., 2009; van Dam et al., 2008; Mora et al., 2007; Smith et al., 2007). These more recent studies are in agreement with all the aforementioned findings observing a median risk reduction of 40% (range 25% to 50%) for coronary heart and cardiovascular diseases when comparing the most active with the least active subjects. However, only 2 of these studies were conducted in populations where the median age of participants was greater than 65 years and only 5 studies included populations with >10% non-white subjects; suggesting areas for further research.

In summary, the data from observational research strongly supports the contention that increased participation in physical activity is associated with reduced all-cause mortality and lowered incidence of coronary artery disease. Even if observational, according to the American Heart Association (Leon et al., 2005) the existing published data satisfy the criteria required to infer a causal relationship (due to the epidemiological scale of the research) and thus physical inactivity is designated a major CHD risk factor (Figure 2.2.1). This, together with further observational studies investigating the association between physical fitness (which is partly determined by physical activity participation) and mortality, result in a convincing argument that physical activity and exercise are fundamental interventions in preventive cardiology practice.

Figure 2.2.1: American Heart Association criteria to infer a causal relationship between physical inactivity and coronary heart disease (CHD) (Leon et al., 2005)

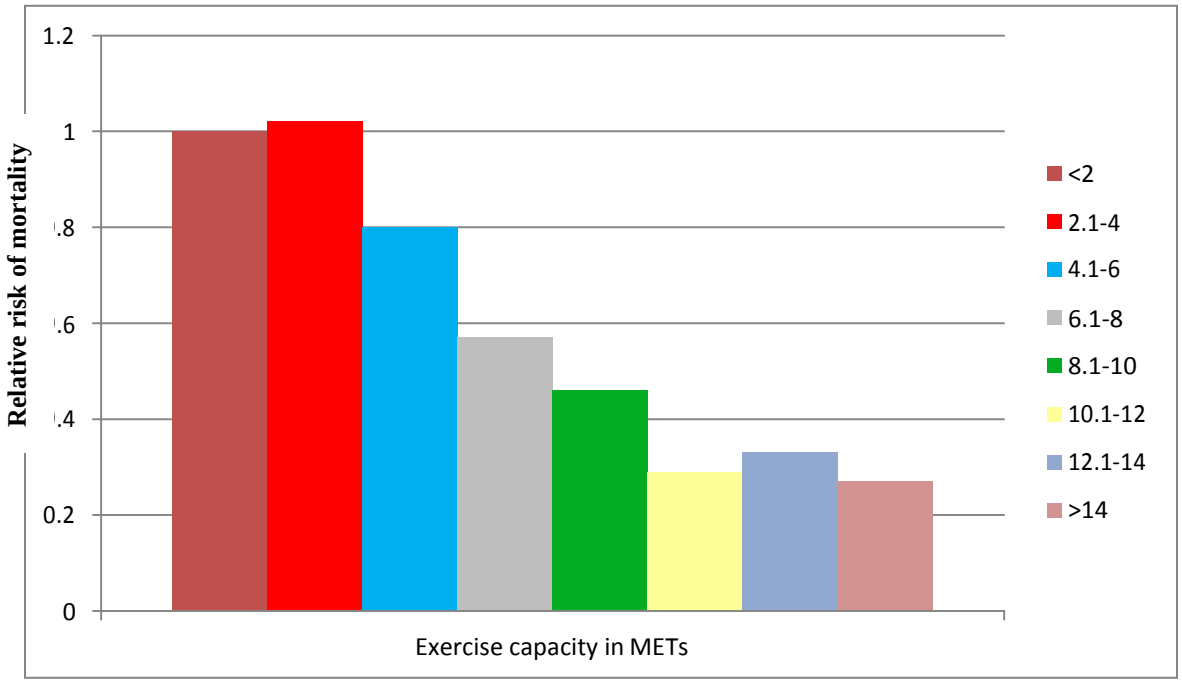
Criteria	Summary
Strength of association	The most physically active individuals have half the CHD rates of those who are sedentary.
Graded relationship	There is a graded relationship of decreasing CHD rates with increasing levels of physical activity.
Consistency of the association	Published studies consistently report lower CHD rates in more physically active individuals.
Temporal relationship	Many of the studies were prospective and demonstrate appropriate sequencing because lower levels of physical activity preceded development of CHD, rather than resulted from the disease itself.
Independence of the association	Multiple studies document the reduced risk for CHD was independent of the presence of other known risk factors.
Biologic plausibility	The results are plausible and coherent with evidence of anti-atherosclerotic, anti-thrombotic, anti-ischaemic, anti-arrhythmic and psychological benefits.

2.2.2: Physical fitness, mortality and cardiovascular disease

Unlike physical activity, which is generally measured by self-report, physical fitness can be measured more objectively. There are many studies examining the association between physical fitness and mortality using maximal exercise testing to quantify fitness, whilst others extrapolate aerobic capacity from sub-maximal tests. The Aerobics Center Longitudinal Study (Blair et al., 1989) was one of the first studies to demonstrate an association between physical fitness and all-cause mortality. 10,224 men and 3,120 women underwent a treadmill test where the „time to exhaustion" was used as a measure of physical fitness. During the 8 year follow-up period there were 240 deaths in men and 43 deaths in women. After adjusting for age, family history of coronary heart disease, smoking status, systolic blood pressure, cholesterol and glucose, the highest quintile in men and those in quintile four for women had the lowest risk of death. These findings would suggest that a high level of physical fitness is associated with longevity.

More recent epidemiological research revealed similar findings by using graded exercise testing as a measure of cardiorespiratory fitness in both black and white men (Kokkinos et al., 2008; Franklin et al., 2004). Based on these studies a lower exercise capacity (< 4 to 5 metabolic equivalents; METs) was associated with a higher risk for all-cause and cardiovascular mortality. Conversely, an exercise capacity of more than 10 METs was associated with the lowest risk for all-cause mortality, even in people with established coronary heart disease (Figure 2.2.2). This is supported by Myers et al., (2002) who investigated 3,679 men with CVD and 2,534 men without CVD using maximal treadmill testing. Subjects were divided into quintiles according to their exercise capacity (METs) and followed up for on average 6.2 years. Again, relative risk for those in the lowest quintile of fitness was four times higher than those in the highest.

Figure 2.2.2: Mortality risk according to exercise capacity (Kokkinos et al., 2008)



Reduced exercise capacity is also associated with an increased risk of death in women. Gulati et al., (2003) studied a cohort of 5,721 healthy women (mean age 52 ± 11 years at baseline) who were categorised into three groups based on their baseline fitness and followed up for on average 8 years. After adjusting for traditional cardiac risk factors using the Framingham Risk Score (Wilson et al., 1998), the risk of death doubled for those in the 5 to 8 METs category and tripled in those in the lowest fitness group (less than 5 METs) when compared with the highest subgroup (exercise capacity greater than 8 METs). These findings support earlier research by Blair et al., (1996) examining the relative risk for all-cause mortality and low fitness together with several other mortality predictors, including smoking, hypertension, hypercholesterolemia and obesity in 25,341 men and 7,080 women. Participants were followed from the baseline assessment for 8.4 years. Low-fit men and women were approximately twice as likely to die during the follow-up period as their more fit counterparts.

One more provocative finding that also emerged from this prospective study by Blair and colleagues (1996) was the notion that fitness is protective against other predictors of mortality. High-fit people with any combination of smoking, hypertension or hypercholesterolemia had lower adjusted deaths rates than low-fit people with none of these risk factors. Barlow et al., (1995) similarly support this concept reporting that it is better to be „fat and fit" versus „lean and unfit", documenting moderate-to-high fit men with a body mass index (BMI) more than 30 $kg \cdot m^{-2}$ had about one third the age-adjusted death rate of lean low-fit men. Several other authors support the hypothesis that physical fitness provides a strong, graded, inverse association with cardiovascular and all-cause mortality independent of BMI, the presence of hypertension and type-2 diabetes (Church et al., 2001; Wei et al., 2000; Wei et al., 1999). This highlights that in the context of preventive cardiology practice where the prevalence of these risk factors is high there are benefits in particularly focussing on exercise training interventions.

Increased cardiorespiratory fitness also appears to offer protection from premature death in people with established coronary artery disease. Kavanagh et al., (2002 and 2003) investigated 12,169 men (55.0 ± 9.6 years) and 2,380 women (59.7 ± 9.5 years) with established coronary heart disease who were referred to a cardiac rehabilitation programme. The men and women were then followed for an average of 7.9 and 6.1 years respectively.

Direct measurement of VO_2 peak, measured during cycle ergometry at programme entry, held significant prognostic value. For each $1mL \cdot kg^{-1} \cdot min^{-1}$ gain in VO_2 peak there was a 9% and 10% reduction in cardiac mortality in men and women respectively. Earlier work by Vanhees et al., (1994) also found significant prognostic value in VO_2 peak in 312 men post myocardial infarction and 215 men following coronary artery bypass surgery. During the 6 year follow-up period there were 53 deaths in total and in 33 of these the cause of death was specifically cardiovascular. Those with the highest cardiovascular and all-cause mortality averaged less than 4.4 METs. Conversely there were no deaths observed in participants whose exercise capacity averaged more than 9.2 METs.

In summary, over the last two decades numerous epidemiological studies in healthy populations and in people with established cardiovascular disease have consistently identified that a low level of physical fitness is an independent risk factor for cardiovascular and all-cause mortality. The risk for all-cause and cardiovascular mortality associated with fitness was similar to that for cigarette smoking and elevated cholesterol levels (Blair et al., 1996). Similar findings have been observed in white and black men, younger and older men and women as well as people with a wide range of pre-existing non-communicable diseases. In view of the above findings, absolute fitness levels, or at least an estimate via sub-maximal testing procedures, holds much clinical value and is consequently should be routinely included in contemporary preventive cardiology practice. Further, the evidence suggests that even small gains in cardiorespiratory fitness hold considerable clinical benefit and consequently exercise training is a key intervention employed in the prevention and management of cardiovascular disease.

2.3: Changes in physical activity, fitness and mortality

Numerous studies in physical activity and fitness suggest that exercise is protective. However, this cannot be assumed given the evidence-base is entirely observational in nature. Another important consideration is that, to a degree, fitness is determined by one‟s genes and a high level of fitness does not necessarily therefore correlate with greater participation in physical activity. Nevertheless increasing physical activity participation at the right dose and mode is associated with increased physical fitness suggesting that individuals can modify their mortality risk by altering their activity levels and thus their fitness. The following will examine the evidence for changes in physical activity or fitness and associated changes all-cause mortality risk.

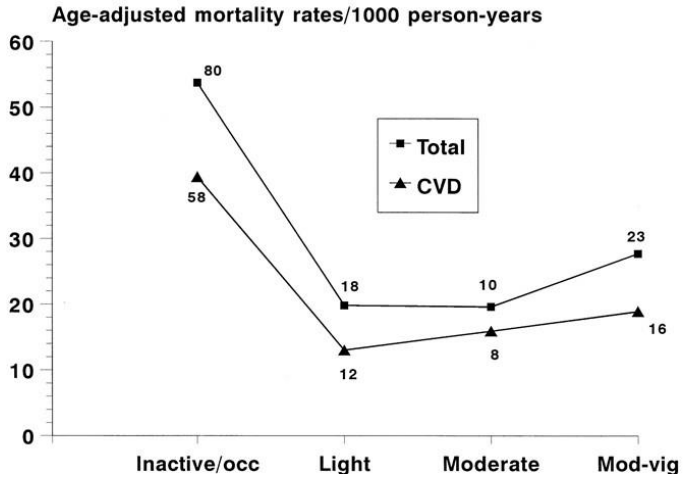
2.3.1: Changes in physical activity and mortality

The Harvard Alumni Health Study (Paffenbarger et al., 1993), which was previously cited, also examined the relationship between change in physical activity and mortality over time. They found a lower mortality rate in those who became more active and/or increased the intensity of their physical activity between the observation points. The highest relative risk of death was seen in those who were previously classified as active (>2000 kcal·week^{-1}) and/or previously participating in more intense physical activity (>4.5 METs) but at follow-up were not achieving either of these two activity thresholds. This highlights the importance of maintaining a physically active lifestyle as past activity levels do not result in lasting protection.

The British Regional Heart Study similarly reported on changes in physical activity and their effects in 7,735 men with and without a wide range of pre-existing cardiovascular disease over a 14 year period. Survivors were subsequently followed up to ascertain 4-year mortality rates (Wannamethee et al., 1998). The beneficial effect of physical activity was seen in both the apparently healthy and those with pre-existing cardiovascular disease. Men who were sedentary at the first observation and who began at least light activity by the last observation had significantly lower all-cause mortality than those who remained sedentary, even after adjustment for potential confounders (risk ratio [RR], 0.55; [95% confidence interval [CI] 0.36-0.84]). Physical activity improved both cardiovascular mortality (RR, 0.66; 95% CI 0.35-1.23) and non-cardiovascular mortality (RR, 0.48; 95% CI 0.27-0.85).

The same group subsequently examined the relationship between physical activity and changes in physical activity over 5 years of follow-up in older men with established CHD and assessed the effects of the common types of physical activity (walking, gardening, and sport) on mortality rates (Wannamethee et al., 2000). The lowest risks for all-cause and cardiovascular mortality were seen in light and moderate activity groups (adjusted relative risk compared with inactive/occasionally active: light, RR, 0.42 (95% CI 0.25, 0.71); moderate, RR, 0.47 (95% CI 0.24, 0.92); and moderately vigorous/vigorous, RR, 0.63 (95% CI 0.39, 1.03) (Figure 2.3.1). Recreational activity of more than 4 hours per weekend, moderate or heavy gardening, and regular walking more than 40 minutes per day were all associated with a significant reduction in all-cause mortality. Importantly, these findings highlight that even light or moderate activities such as walking and gardening can contribute to a lowered risk of all-cause mortality in older men.

Figure 2.3.1: Physical activity at final observation and age-adjusted mortality rates per 1000 person-years in 772 men with established cardiovascular disease (Wannamethee et al., 2000).



A reduced risk of all-cause mortality is also consistently seen for older women. Gregg et al., (2003) examined the relationship of changes in physical activity and mortality prospectively in 9518 older women aged 65 years or older. Walking and other physical activities were assessed at baseline using self-report (1986-1988); 7553 of whom were reassessed at a follow-up visit on average 5 years later (1992-1994). The women were tracked for up to 12.5 years after baseline (up to 6.7 years after the follow-up visit). Similar to the findings in men, when compared with sedentary women, those who increased physical activity levels between baseline and follow-up had lower mortality from all causes (hazard rate ratio [HRR], 0.52; 95% CI, 0.40-0.69), cardiovascular disease (HRR, 0.64; 95% CI, 0.42-0.97), and cancer (HRR, 0.49; 95% CI, 0.29-0.84), independent of age, smoking, body mass index, co-morbid conditions, and baseline physical activity level. Associations between changes in physical activity and reduced mortality were similar in women with and without chronic diseases. Women who were physically active at both visits also had lower all-cause mortality (HRR, 0.68; 95% CI, 0.56-0.82) and cardiovascular mortality (HRR, 0.62; 95% CI, 0.44-0.88) than sedentary women.

In summary, several cohort studies, using repeated measurements, have consistently demonstrated that previously sedentary individuals who increase their physical activity levels live longer than their persistently sedentary counterparts. Importantly, this is after adjusting for possible confounders that may also explain this clinical benefit. This is of major relevance to preventive cardiology practice where a high proportion of individuals, many of them older adults and with pre-existing disease, are sedentary and therefore there is much to gain from a structured programme that includes an activity increasing intervention.

2.3.2: Changes in physical fitness and mortality

Given the above findings, we would expect improvements in physical fitness to concomitantly reduce the risk of cardiovascular and all-cause mortality. The Aerobics Longitudinal Study by Blair et al., (1995) was one of the first landmark studies to support this argument. This study included a follow-up fitness test allowing for the relationship between changes in fitness and mortality to be evaluated. They found that those in the lowest quintile for performance initially but had improved their fitness when assessed 5 years later, experienced a 52% lower age-adjusted risk of cardiovascular mortality than men who remained unfit.

Moreover, those in quintile two and three who increased their fitness further had a 28% lower risk of cardiovascular mortality than their reasonably fit counterparts whose fitness remained the same over time. In both cases these benefits in lowered mortality remained after adjusting for other risk factors at baseline and changes in risk factors during follow-up.

These findings are supported by more recent research in a meta-analysis pooling 33 epidemiological studies investigating the relationship between level of cardiorespiratory fitness (CRF) and all-cause mortality (n=102,980) and incidence of CHD and CVD (n=84,323) (Kodama et al., 2009). Participants were categorised as low CRF (< 7.9 METs), intermediate CRF (7.9-10.8 METs), or high CRF (> or = 10.9 METs). Compared with participants with high CRF, those with low CRF had a risk ratio for all-cause mortality of 1.70 (95% CI, 1.51-1.92; P<.001) and for CHD/CVD events of 1.56 (95% CI, 1.39-1.75; P < .001). Compared with participants with intermediate CRF, those with low CRF had a risk ratio for all-cause mortality of 1.40 (95% CI, 1.32-1.48; P < .001) and for CHD/CVD events of 1.47 (95% CI, 1.35-1.61; P<.001). In both cases these findings were adjusted for heterogeneity of study design. Consequently, the overall aim for a preventive cardiology programme therefore is to achieve a capacity of at least 7.9 METs in order to substantially lower rates of all-cause mortality and CHD/CVD events.

These findings would suggest that people have an element of control over their own mortality and even small gains in fitness hold benefit. Exercise performance data from Myers et al., (2002) would suggest that every 1 MET increase in exercise capacity conferred a 12% improvement in survival in men with and without cardiovascular disease. Similarly in women, Gulati et al., (2003) demonstrated a 17% reduction in mortality rate for every 1 MET increase. Of note; this was seen previously in the study by Blair et al., (1995) using a repeated measures design they found that for every 1 MET improvement in fitness, there was an estimated reduction of 16% in mortality risk.

Looking beyond observational data, one randomised controlled trial examined whether a supervised exercise program improved 19-year survival in 30 to 64 year old male myocardial infarction patients (Dorn et al., 1999).The men (n=651) were participants in the National Exercise and Heart Disease Project, a 3-year multicentre randomised clinical trial conducted in the United States (1976-1979). The treatment group (n=315) exercised for 8 weeks in the laboratory. Thereafter, they jogged, cycled, or swam in a gymnasium or pool setting, guided by an individualised target heart rate. Participants in the control group (n=319) were to maintain normal routines but not participate in any regular exercise programme. Participants were followed up until their death or until December 31, 1995.

Exercise-programme participation resulted in non-significant reductions in mortality risk early in the follow-up period, with effects diminishing over the longer term. The all-cause mortality risk estimates (95% CIs) in the exercise group compared with controls was 0.69 (0.39 to 1.25) after an average follow-up of 3 years, 0.84 (0.55 to 1.28) after 5 years, 0.95 (0.71 to 1.29) after 10 years, 1.02 (0.79 to 1.32) after 15 years, and 1.09 (0.87 to 1. 36) after 19 years. Cardiovascular disease (CVD) mortality risk estimates (95% CI) for the same follow-up periods were 0.73 (0.37 to 1.43), 0.98 (0.60 to 1.61), 1.21 (0.79 to 1.60), 1.14 (0.84 to 1.54), and 1.16 (0.88 to 1.52).

However, each 1-MET increase in work capacity from baseline to the end of the original trial resulted in consistent and significant reductions in all-cause and CVD mortality risk at each follow-up period, regardless of initial work-capacity level in both the intervention and the control group. This clearly illustrates the limitations of randomised controlled trials (RCT‟s) in the context of lifestyle behaviours. Whilst RCT‟s are the gold standard in providing the most compelling evidence for a cause and effect relationship, they are particularly challenging in behavioural medicine given the difficulty in controlling factors such as activity in the control group. „Contamination‟, as a result of uncontrollable factors, could easily explain the diminished effects. This same study, using its observational data, demonstrated that increased work capacity provided survival benefits for up to 19 years (Dorn et al., 1999).

In closing this theme, numerous epidemiological studies have demonstrated a reduction in mortality risk per MET gained; ranging between 10% and 25%. This is evident in both young and elderly people, men and women and individuals with and without documented cardiovascular disease. In the Veterans Exercise Testing Study, similar findings have been observed among the elderly with multiple risk factors and among Black Americans (Kokkinos et al., 2008). In the latter group, a 15% lower mortality risk was reported for every 1 MET increase in exercise capacity, similar to that observed in Caucasians. Collectively these studies have consistently identified a low level of cardiorespiratory fitness as an independent risk factor for all-cause and cardiovascular mortality. In general, it would appear that the highest risk of mortality is in those with an exercise capacity less than 5 METs. Consequently it is important that interventions aimed at improving physical activity and fitness levels consider the optimal exercise type, duration, intensity and volume in order to gain the greatest associated reductions in mortality risk.

2.4: Measurement of physical activity and fitness

There is compelling evidence as to the benefits of both physical activity participation and physical fitness (Sections 2.2 and 2.3) and therefore in the context of this study it is justified to include measures for both. In relation to the former, physical activity behaviour is complicated and dynamic, resulting in challenges in its measurement. Typically epidemiological studies, such as the large prospective cohort studies earlier, most commonly use questionnaires. However, there are many methods available to measure physical activity; some more suited to particular study designs and others to everyday clinical practice. In relation to the latter, cardiorespiratory fitness can be measured directly through exercise testing or alternatively through surrogate measures that are designed to predict aerobic capacity. The following section aims to review the literature with the purpose of providing the rationale for the measures selected in this study.

2.4.1: Overview of methods available to measure physical activity and fitness

The gold standard methods to assess physical activity are by criterion methods such as „doubly labelled water" (DLW), indirect calorimetry and direct observation. These are considered the most reliable and valid measurements against which all other physical activity assessments methods should be validated, but they also hold important drawbacks (Vanhees et al., 2005). The doubly labelled water method (DLW) is a variant of indirect calorimetry and is applicable to both laboratory and field studies. The strength of this method is that metabolic processes are measured, which are directly related to physical activity. However, production and analysis of the isotopes required is expensive and therefore not suitable for large-scale studies. Indirect calorimetry also measures energy expenditure but requires even more expensive equipment such as a ventilation hood or a respiration chamber (Starling, 2002). Like DLW, indirect calorimetry has too many practical problems to apply on a large sample. Unfortunately, direct observation is also a very time-consuming and tedious job and is therefore not convenient for large-scale studies (McKenzie, 2002). Given the nature of this study these methods are not appropriate and will not be further reviewed.

In addition to the criterion measures presented above, other examples of tools used to quantify physical activity include subjective measures that rely on physical activity recall (e.g. self-administered and interview-administered questionnaires, activity diaries) and objective measures that sense movement (e.g. pedometers and accelerometers).

Health-related physical fitness includes cardiorespiratory capacity, body composition, muscular strength and flexibility; and each of these can be measured. To name but a few: cardiorespiratory capacity is determined through direct measurement using exercise testing; body composition by body mass index, bioelectric impedance and body folds; strength by one repetition maximum; and flexibility by a sit and reach test. In relation to preventive cardiology practice there is particularly strong evidence linking cardiorespiratory fitness (Section 2.2 and 2.3) and therefore measurement of this component will be the primary focus.

For the assessment of cardiorespiratory fitness, there are a wide range of field tests and laboratory tests available. In the laboratory, exercise capacity is preferentially assessed through maximal incremental exercise testing. Cardio-pulmonary exercise testing is a well-established procedure that provides a wealth of clinically diagnostic and prognostic information. The peak oxygen uptake, through direct measurement, is the gold standard in the assessment of exercise tolerance. Maximal exercise testing however is costly and carries some risk of adverse events and consequently cardiorespiratory capacity can be indirectly quantified through sub-maximal testing. Finally there are also surrogate measures of fitness such as the use of self-reported functional questionnaires to estimate maximal oxygen uptake (e.g. the Duke Activity Status Index (DASI) questionnaire by Hltaky et al., 1987).

Given this study is a demonstration programme; this review will focus on exploring direct and indirect measures that are practical and can be applied in the context of a preventive cardiology programme being delivered in everyday clinical practice. Surrogate measures will not be considered.

2.4.2: Questionnaires to measure physical activity

Questionnaires for assessment of physical activity are the most common method and there are currently hundred of variants available (Welk, 2002; Kriska & Caspersen, 1997). The most basic of these classify people as active or inactive, based simply on two or three questions. Whilst this is highly practical, especially in population studies, physical activity is a complex behaviour. The dose (or volume) of any type (or mode) of an activity is comprised of its frequency, intensity and duration and consequently it becomes impossible to comprehensively capture all this information in just two or three questions. As a result this introduces bias and imprecision resulting in a high chance of misclassification.

In addition to the authors above, Pereira et al., (1997) and Washburn and Monotype (1986) have both published descriptions of a collection of physical activity questionnaires together with information concerning their reliability and validity. Questionnaires vary considerably on several important factors: the period of time over which activity is assessed; the intended population e.g. adults, older adults, adolescents; type of activity assessed e.g. leisure, household, transportation, occupation; length of questionnaire; administration mode e.g. interview or self-administered; and

outcome measurement e.g. kilocalories, MET-hours. For that reason there are many considerations when selecting an appropriate questionnaire. It is essential that the questionnaires selected are sensitive and can be generalised to the population being assessed. Some questionnaires focus on occupational activity and would therefore not be suitable for a retired older adult; others focus on leisure activity, which may underestimate activity in an older adult doing less structured activity and more activities of daily living, such as gardening.

In order to assess engagement in physical activity, researchers typically ask participants about their usual activity. However, often study designs require participants to recall their past physical activity levels. For example in a case-control study of breast cancer, women aged between 36 and 40 years of age were asked to recall their participation in sports and leisure activities when they were 10, 16 and 25 years old (Hardman & Stensel, 2009). Recalling activity over a long period of time in this way is likely to be subject to a large degree of error. Conversely, reporting activity over a recent and defined period, such as the previous week, improves the accuracy but the validity of the data is limited by the extent to which the period sampled reflects each individual‟s typical activity behaviour.

Further, if exercise or training habits are asked about, it should be noted that the respondent only assesses parts of the total physical activity completed. These questions most often show a high degree of reliability and validity, since it is easier to remember what is done regularly and with a higher intensity (Katmarzyk & Craig, 2002; Nelson et al., 2007; Neilson et al., 2008). It is also exercise that has shown the strongest association to achieved health effects. If exercise is prescribed, then it is also exercise that should be evaluated. However, if everyday activities are prescribed, they cannot be assessed with questions about exercise.

As reported by Hardman and Stensel (2009), the precision (or repeatability) of questionnaires, assessed by test-retest correlation coefficients is high; typically exceeding 0.75 when tests are within one month. A further benefit is that questionnaires have been validated using a number of measures including cardiorespiratory fitness, motion sensors (usually accelerometers) and the DLW method described above (Neilson et al., 2008; Sallis & Saelens, 2000). Whilst a modest relationship exists between physical activity scores and fitness (typically with correlation co-

efficient values in the range of 0.3-0.5), questionnaire measures do not correlate well with accelerometer recordings or total energy expenditure from the gold-standard DLW technique (Hekler et al., 2012; Robinson-Cohen et al., 2013; Lee et al., 2011).

However, before drawing any strong conclusions some of these comparisons may not be entirely appropriate. For example, a questionnaire designed to assess leisure time physical activity is unlikely to correlate well with the DLW method; the latter captures all volitional and non-volitional activity thereby measuring total energy expenditure and not a specific single domain. Despite the limitations of questionnaires they are the most practical and often-used method of assessing physical activity; primarily because of low financial cost and low participant burden (Appendix 4).

A review by Sallis and Saelens (2000) concluded there are several self-report techniques with adequate reliability, content validity and relative criterion validity. Interview measures tended to have stronger psychometric characteristics than self-administered measures. The same authors also found that individuals tended to overestimate participation in vigorous activities and underestimate light-to-moderate intensity activities.

In the context of preventive cardiology practice, self-reported measures of physical activity provide useful information in gaining an understanding of each individual‟s previous and current activity participation, as well as providing an insight into activities that are both enjoyable and of interest to sustain compliance. By observation of activity over a period of a week (e.g. by an activity log or 7-day activity recall) the physical activity specialist can determine whether individuals are achieving the current recommended levels of activity as well as quantify energy expenditure. This review has identified that there are many limitations in the use of physical activity questionnaires. None the less, they are very practical and low cost. In summary, whilst there are hundreds of questionnaires available, the data would suggest an interview administered recall of activities over the past week (that must include both general physical activity and exercise) offers a higher degree of validity and reliability than these self-administered questionnaires (Shepherd, 2003).

2.4.3: Motion sensors to measure physical activity

Motion sensors have become one of the most popular means of assessing physical activity. Both types of motion sensors (pedometers and accelerometers) are objective alternatives to self-reports of activity behaviour (Hardman & Stensel, 2009). One advantage of these devices over the traditional self-report instruments such as physical activity logs, diaries, and questionnaires is that pedometers and accelerometers are less subjective. They are not prone to the same systematic errors as they do not depend upon a person‟s recall ability, whereas self-report instruments, as highlighted above, rely heavily on a person‟s ability to judge the frequency, intensity, and duration of activity bouts.

Pedometers operate using a spring-suspended lever that measures „counts‟ of movement in the vertical plane. They provide a rough measure of the activity and there are many different brands of varying quality. Depending on sensitivity, the variation in the number of steps can be more than 20 per cent (Schneider et al., 2004). The disadvantage of step-counters primarily lies in the fact that they say nothing about intensity. This means that if a person walks 100 meters, the step-counter will register approximately 110 steps, while it only registers approximately 70 steps if the person runs. Nevertheless, they do count steps taken with acceptable accuracy.

Conversely, accelerometers are more advanced instruments with greater precision. Akin to the pedometer, most accelerometers measure acceleration only in the vertical plane and are consequently described as uni-axial in nature. However, there are a growing number of models designed to measure accelerations in three planes, described as tri-axial, thereby providing a more comprehensive assessment of body movement. Besides total physical activity, accelerometers can also provide a measure of intensity, duration and frequency, and consequently are superior in assessing the pattern of the activity.

Accelerometers report, via computer outputs, „counts‟ in a range of speeds together with duration which allows the researcher to describe energy expenditure or time spent in moderate to vigorous activity. Another advantage is that accelerometers can also quantify inactivity and sedentary behaviour (Ward et al., 2005). However, accelerometers are more costly than step-counters, but they are preferable if greater precision is desired.

Both step counters and accelerometers are insensitive to activities that take place with the upper-body or activities such as swimming and cycling. In spite of this, they provide a good view of overall activity, and for accelerometers also of how the activity is divided over the day. Studies have shown that approximately 90 per cent of the time is spent sitting, standing and walking; hence motion sensors can register the vast majority of activity (Schneider et al., 2003; Ward et al., 2005).

Bassett and John (2010) recently reviewed a number of activity monitors, including four pedometers (Yamax SW digi-walker, New Lifestyles NL-2000, Omron HJ-720 ITC, and StepWatch) (Figure 2.4.1), three accelerometer-based activity monitors (ActiGraph, Actical, and RT3), and a multi-sensor device (Sensewear Armband). Validity and reliability of each of these devices were explored. The Yamax SW digi-walker was found to be the most widely used pedometer in research studies. Previous studies comparing 10 or more pedometer models identified it as one of the most accurate and reliable electronic pedometers available (Schneider et al., 2004; Crouter et al., 2003; Schneider et al., 2003).

Figure 2.4.1: Pedometer devices reviewed by Bassett and John (2010)

Yamax pedometer
Model SW-200

New Lifestyles
NL-2000

Omron
HJ-720 ITC

StepWatch

The Yamax SW-200 pedometer is a simple step counter, costing approximately £15 per device, with a single button that resets it to zero. Further positive features include its plastic cover that can be secured shut to prevent resetting, and also to minimise pedometer „reactivity". Reactivity refers to a change in physical activity that results when an individual is allowed to view his or her activity data (Karabulut et al., 2005), and is considered undesirable when collecting baseline data. Moreover, due to its wide use in research, it is possible to compare descriptive data (steps

per day) for specific age groups, cultures, and clinical populations. Tudor-Locke and Bassett (2004) have proposed useful step indices based on data collected with the Yamax digi-walker:

Figure 2.4.2: Tutor-Locke and Bassett (2004) Categorisation of Steps per Day

<5,000	**Sedentary**
5,000-7499	**Low active**
7500-9999	**Somewhat active**
10,000-12,499	**Active**
>12,500	**Highly active**

In contrast, the Yamax pedometer has a tendency to undercount steps, thereby reducing validity. At 1.5 miles/hour (mph) it records 75% of actual steps, and at 2.0 mph it records 88% of actual steps (Crouter et al., 2003; Karabulut et al., 2005). In addition to slow walking, the Yamax digi-walker also undercounts steps to a greater degree in obese populations (Crouter et al., 2005; Melanson et al., 2004). On the other hand over-counting errors are rare, but can occur when driving motor vehicles. The Yamax digi-walker records 6–10 erroneous steps while driving a distance of 10 miles (Le Masurier & Tudor-Locke, 2003).

A new finding in the past decade is that pedometers and accelerometers are not only useful as measurement tools, but they can also motivate sedentary people to increase their activity level (Tudor-Locke, 2002). This is strongly supported by a systematic review by Bravata et al., (2007) which included 26 studies with a total of 2767 participants. In the eight RCTs included, pedometer users significantly increased their physical activity by 2491 steps per day more than control participants (95% CI, 1098 to 3885 steps per day, $P < .001$). Among the remaining observational studies, similarly pedometer users significantly increased their physical activity by 2183 steps per day over baseline (95% CI, 1571 to 2796 steps per day, $P < .0001$). In general, pedometer users increased their physical activity by 26.9% above baseline highlighting their effectiveness as an intervention for increasing physical activity.

In summary, devices to monitor physical activity have become more sophisticated and accurate in recent years. While some devices require research participants to record the data each night in an activity log, newer devices have sufficient battery life and memory capacity to store minute-by-minute activity data over several weeks, which can be subsequently downloaded to a computer (Bassett & John, 2010). For motivational purposes, a simple, low-cost step counter may suffice, and these are much more feasible from a cost standpoint. However, if the desired outcome variable is a measure of energy expenditure then accelerometer-based devices are advantageous as they provide a more objective indicator given their ability to quantify activity intensity. However, accelerometers are costly and hence the more affordable pedometer can be considered as a more limited but suitable alternative. Pedometers should only be used in individuals where walking is their main reported activity. Careful selection of pedometer model is important as some devices offer greater precision. Following review, the Yamax digi-walker SW-200 is the most widely accepted model of pedometer for research purposes.

2.4.4: Cardiorespiratory fitness

As highlighted in Section 2.2, numerous epidemiological studies on healthy populations and those with established cardiovascular disease have consistently identified that a low level of physical fitness is an independent risk factor for cardiovascular and all-cause mortality. Direct measurement of maximal oxygen uptake (VO_2max) is considered the gold standard with respect to measurement of cardiorespiratory fitness and is most commonly made during cycle ergometry or treadmill walking or running. The American College of Sports Medicine (2006) recommend that maximal tests should not be carried out on risk individuals other than under controlled forms, such as in a physiological laboratory. Consequently, maximal exercise testing has practical constraints in the preventive cardiology setting.

There is a strong linear relationship between oxygen uptake and heart rate with incremental exercise workload and so it is possible to directly estimate maximal oxygen uptake by extrapolation from a sub-maximal test. For this reason submaximal tests are very well suited to clinics and in prevention and promotion work. All submaximal tests build on the same principle that there is a linear relationship between exercise intensity and heart rate. With the help of the

maximal heart rate (which can be calculated by a prediction based on age) and a known workload, the maximal oxygen uptake can be calculated (ACSM, 2013).

Submaximal exercise testing dates back, at least, to the 1940s with the Harvard Step Test for estimating fitness in large swathes of army recruits (Brouha et al., 1943). The 1950s welcomed the addition of predictive nomograms for cycle ergometry and box stepping (Astrand & Ryhming, 1954). In the 1970s McGavin (1976) adapted Cooper‟s 12 minute run test (Cooper, 1968) into a 12 minute walk test for pulmonary disease patients, which was later shown by Butland et al. (1982) to be just as valid if performed over six minutes; resulting in the birth of the 6-minute walk test (6-MWT). In 1985 Guyatt et al. validated the 6-MWT for use with heart failure patients.

The above indicates there are numerous sub-maximal cycle, stepping and walking or running based protocols available for assessing aerobic capacity. Protocols that require costly equipment, such as cycle ergometers or treadmills, will not be considered as these are beyond the economic realms of this study. Given the population concerned, it is of relevance to consider exercise testing protocols that are acceptable for people with established cardiovascular disease, such as post myocardial infarction, as well as apparently healthy individuals presenting with multiple risk factors for heart attack or stroke.

There are particular advantages to walking tests as they offer the most familiarity and can accommodate people with low levels of function. The 6-MWT assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity (ATS, 2002) and has been investigated in a number of clinical populations: Alzheimer‟s disease, children fibromyalgia, geriatrics, heart failure, multiple sclerosis, Parkinson‟s disease, pulmonary disease, osteoarthritis, spinal cord injury, cardiac rehabilitation and stroke.

In relation to populations with established CVD, Bellet et al., (2012) carried out a systematic review of the validity, reliability and responsiveness of the 6-MWT in cardiac rehabilitation. Fifteen articles met the inclusion criteria. One high-quality study was identified for reliability, six high-quality studies were identified for validity and 11 high-quality studies were identified for responsiveness. The meta-analysis found strong evidence that the 6-MWT was responsive to

change in clinical status following cardiac rehabilitation. There was moderate evidence for repeatability of the 6-MWT in patients undergoing cardiac rehabilitation and likewise a moderate correlation between the 6-minute walk distance and maximum metabolic equivalents achieved on symptom-limited exercise tests. This systematic review concluded that the validity of the 6-MWT in patients undergoing cardiac rehabilitation requires further research.

There is however data to suggest that the 6-MWT performs better in low functioning patients. For example, a large systematic review by Pollentier et al., (2010) reported good reliability, moderate validity, and a significant ability to predict functional capacity in patients with chronic heart failure who do not walk greater than 490 meters. In those that can manage greater distances the validity of the 6-MWT as a predictor of aerobic capacity reduces.

In 1992 Singh et al. developed the Incremental Shuttle Walk Test (ISWT) for pulmonary patients, which was externally paced by incremental bleeps and aimed to eliminate problems of self-pacing found in the 6-MWT. The ISWT was derived from the incremental shuttle run tests designed for athletes (Leger & Lambert, 1982; Ramsbottom et al., 1988) and is now commonly used in both pulmonary and cardiac rehabilitation populations.

A recent systematic review by Parreira et al., (2014) identified 800 articles describing the measurement properties of the ISWT in a clinical population. The vast majority of these were of poor quality and only 35 articles were included. Twenty-one articles included data on the validity of ISWT, 18 on reliability, four on responsiveness and four on interpretability. Most of the studies were conducted in patients with chronic obstructive pulmonary disease (n=13) or cardiac disease (n=8). For criterion validity, comparisons between distance covered during the ISWT and peak oxygen uptake reported correlations ranging from 0.67 to 0.95. For reliability, intra-class correlation coefficients for test-retest ranged from 0.76 to 0.99. They concluded the ISWT can be considered a valid and reliable test to assess maximal exercise capacity, particularly in pulmonary patients.

Part of this study also includes a cohort of asymptomatic individuals presenting with cardiovascular risk factors and an aggregate score that calculates them to be at high risk of a heart attack or stroke in the next 5-10 years. This group have not been well studied in the context of either the 6-MWT or the ISWT. There is some data, albeit limited, for the Chester Step Test (CST) (Sykes, 1998). Whilst there are no systematic reviews of the CST available to date, findings from several authors would indicate this test may be useful for the assessment and management of CVD risk in a clinical setting (Stevens & Sykes, 1996; Buckley et al., 2004; Buckley & Jones, 2011; Cooney et al., 2013).

All submaximal aerobic fitness tests have a minimum of 10–15 per cent method error and can be used on the individual level before and after an intervention if the conditions are standardised (FYSS, 2010). The error margin is smaller for the CST than for walking or running based bleep tests (Stevens & Sykes, 1996). This is most likely a consequence of a standardised step height coupled with external pacing to cue the exact timing for every step taken. The systematic errors are largely due to the assumption made about the individual‟s maximal heart rate, but also to full stroke volume not being achieved and any handling errors, such as the speed, height or resistance not being calibrated.

Despite this error margin, submaximal tests still give a reasonably accurate reflection of an individual's fitness without the cost, time, effort and risk on the part of the subject. While all these tests have inherent advantages and disadvantages (Appendix 4), when used correctly they can provide valuable baseline data about the fitness levels of individuals and data from which exercise programmes may be developed. The tests also enable fitness improvements to be monitored, help to motivate participants by establishing reasonable and achievable goals, assist in risk stratification and facilitate participants' education about the importance of physical fitness for work and for life (Buckley & Jones, 2011). Consequently, including an evaluation of cardiorespiratory fitness in preventive cardiology practice holds enormous value and in the context of this study is essential.

2.4.5: Summary

Regular aerobic physical activity increases exercise capacity and physical fitness, which can lead to many health benefits. Accurate quantification of both physical activity and physical fitness becomes essential in terms of health outcome and effectiveness of intervention programmes. Three types of physical activity assessment methods can be distinguished: criterion methods, objective methods and subjective methods. Criterion methods like doubly labelled water, indirect calorimetry and direct observation are the most reliable and valid measurements but they also hold important drawbacks. Objective assessment methods include activity monitors (pedometers and accelerometers) and there are many models available on the market. With regards to pedometers the Yamax SW-200 model is one of the most widely used in research. Finally self-reported activity is the most inexpensive of all the tools available and is easily applicable to large populations. However these methods are fought with difficulties as they are influenced by many different factors (e.g., recall bias, social desirability, age, complexity of the questionnaire, seasonal variation, length of period surveyed) (Van Hees et al., 2005; Warren et al., 2010).

With regards to measurement of cardiorespiratory fitness, direct measurement of peak oxygen uptake is the gold standard but not a feasible option for this study. This review identifies that an estimation of aerobic capacity extrapolated from a submaximal test offers a reasonable alternative. Looking to the lower cost options (given the economic confines of the study) the Incremental Shuttle Walk Test and Chester Step Test are advantageous as they have been evaluated in the same populations as this study.

Essentially this review has highlighted that the perfect assessment method does not exist (Appendix 4). As identified in a recent review by Warren and colleagues (2010), selection of a method must therefore be based on careful consideration of its pros and cons, indications for use and the evidence to support it. It is acknowledged that the choice of method may be a compromise between accuracy level and feasibility, but the ultimate choice of tool must suit the stated aim of the research.

2.5: Factors contributing to the cardioprotective effects arising from aerobic exercise training

It is clear from epidemiological studies that leading a physically active lifestyle and higher levels of cardiorespiratory fitness are associated with improved health outcomes. Supporting evidence of causative relationships has demonstrated multiple plausible cardioprotective biological mechanisms that explain the association between aerobic exercise and reduced incidence of cardiovascular disease. These include direct anti-atherosclerotic effects by improving artery endothelial function and reducing inflammation and indirectly via modification of other risk factor components of the metabolic syndrome. This reduces the risk of a coronary thrombotic occlusion (anti-thrombotic effects), by decreasing myocardial oxygen demands and increasing its vascular supply (anti-ischemic effects). Cardiomyocyte electrical stability is also improved as are autonomic nervous system adaptations (anti-arrhythmic effects) (Figure 2.5.1).

Although much additional research is needed to better define and establish optimal dose-response relationships, clearly these pleotropic effects strongly suggest that aerobic exercise can attenuate the risk of coronary heart disease at all stages of the underlying atherothrombotic process (Leon, 2009). Recent data from the CARDIA study revealed healthy lifestyle changes during young adulthood are associated with decreased (and unhealthy lifestyle changes with increased) risk for subclinical atherosclerosis in middle age (Spring et al., 2014). This section of the review will discuss the atherosclerotic process in brief and these protective biological mechanisms associated with aerobic exercise in more detail.

2.5.1: The atherosclerotic process in brief

Atherosclerotic disease is in part a result of chronic inflammation caused by an interaction between modified lipoproteins and components of the immune system. The process begins during childhood and is initiated by multiple risk factors, which cause injury to artery endothelial linings. This results in a cascade of pathophysiological events, including lipid infiltration, primarily of low-density lipoprotein (LDL), and its subsequent oxidation (Leon, 2009). This triggers a progressive inflammatory response, resulting in formation of plaques and progressive narrowing of the artery. However, some plaques are vulnerable and disruption initiates platelet aggregation and thrombus formation at the damage site, causing complete arterial occlusion,

which results in myocardial infarction (coronary occlusion), stroke (cerebral occlusion) or peripheral arterial disease. The determinants and risk factors underlying the atherosclerotic process include non-modifiable and modifiable factors (Figure 2.5.2). The inverse association of physical activity and cardiovascular disease has been demonstrated in both men and women by an extensive body of epidemiologic observational studies. Strong supporting evidence for the cardioprotective effects has been provided by experimental work in animals and humans. The following will concentrate primarily on coronary heart disease and the anti-atherosclerotic, anti-thrombotic, anti-ischaemic and anti-arrhythmic effects. These biological mechanisms support the notion that exercise is a powerful „medicine" in the prevention and management of many health disorders.

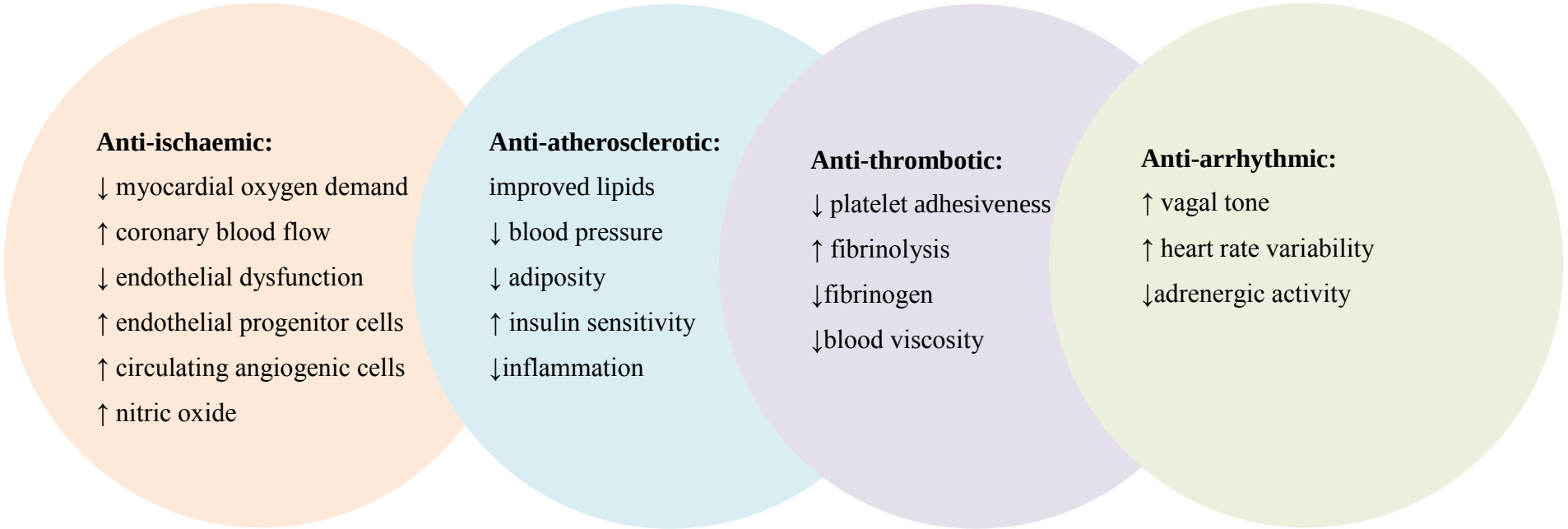


Figure 2.5.1: Cardioprotective mechanisms associated with regular exercise training (Franklin & Gordon, 2009)

Figure 2.5.2: Risk factors and determinants for atherosclerosis

Biological	**Lifestyle Determinants**	**Broader Determinants** Fixed	Modifiable
Raised blood pressure Raised blood sugar Raised blood cholesterol Overweight/obesity	Tobacco use Unhealthy diet Alcohol abuse Physical inactivity Stress Depression	Age Sex Genetics Ethnicity	Income Education Living conditions Working Conditions

2.5.2: Anti-atherosclerotic effects

There is strong support for the concept that exercise can reduce the progression of lesions and contribute to the partial regression of atherosclerotic plaques (Leon, 2009). In a prospective study using the gold standard; angiography to measure plaque size, 18 angina patients received exercise training (3 hours per week) and a low fat calorie controlled dietary intervention. They were compared at 1 year to 18 subjects from „usual care" (control); 7 out of 18 subjects in the intervention group experienced significant plaque regression compared to only 1 out of 18 in the control group ($p<0.05$) (Schuler et al., 1992). This is powerful data suggesting that regular "physical exercise" and a low fat diet may retard (and to a degree reverse) progression of coronary artery disease. However, this was a small study population with no random allocation to the treatment group and the effect size of the exercise component in isolation remains unknown.

Rauramaa et al., (2004) investigated the long-term effects of mild to moderate intensity aerobic exercise on atherosclerosis and inflammatory markers over a 6 year period in 140 middle-aged white men randomly selected from the population registry. They objectively measured carotid intima-media thickness and found no significant difference overall. However in a subsample of the intervention group (those not taking a statin) there was a 40% difference in the exercise intervention group (0.12 mm [95% CI, -0.010 to 0.26 mm]) compared to the control group (0.20 mm [CI, 0.05 to 0.35 mm]). This indicates potential benefit in patients who are sub optimally managed from a medication viewpoint; perhaps those with statin intolerance. However, given contemporary clinical practice where the majority of patients with cardiovascular disease are prescribed a statin, with rare intolerance, these findings have limited applicability.

Another anti-atherosclerotic property of exercise training is its favourable effects on lipid and lipoprotein metabolism. The most consistent findings are of an increase in the protective high density lipoprotein (HDL) cholesterol. Well conducted observational studies reveal a positive dose-response association between level of activity and HDL concentration (Williams, 1996; LaPorte et al., 1983). Randomised controlled trial data from the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise (STRRIDE) concurs (Slentz et al., 2007; Kraus et al., 2002). Sedentary, overweight subjects (n = 240) were randomised to 6 months control or one of three exercise groups: 1) high-amount/vigorous-intensity exercise; 2) low-amount/vigorous-intensity exercise; or 3) low-amount/moderate-intensity exercise. Training consisted of a gradual increase in amount of exercise followed by 6 months of exercise at the prescribed level. The high-amount group had significant improvements in high-density lipoprotein (HDL)-cholesterol, HDL particle size, and large HDL levels that were sustained for 15 days after exercise stopped. In essence, thirty minutes per day of vigorous exercise, like jogging, has sustained beneficial effects on HDL metabolism.

Other anti-atherosclerotic properties associated with aerobic exercise include: endothelial repair and regeneration; promotion and prolongation of synthesis and effect of nitric oxide (a powerful vasodilator) and reduction in the circulation of inflammatory biomarkers, such as C-reactive protein (Leon, 2009). Moreover, aerobic exercise is also associated with weight reduction, in particular visceral fat, which is closely associated with several metabolic disorders, including cardiovascular disease (Myers, 2003).

2.5.3: Anti-thrombotic effects

The vast majority of acute coronary syndromes are initiated by a thrombus-induced coronary occlusion. Improved endothelial function is associated with activity. Exercise training reduces platelet aggregation and a number of blood clotting factors, including fibrinogen, and it promotes fibrinolysis by increasing activity of endothelial plasminogen activator (Leon, 2009; Wang, 2006). In a RCT including 140 middle-aged overweight men, aerobic exercise was shown to reduce blood coagulation (Rauramaa et al., 1986). This study assessed the influence of regular moderate-intensity "physical exercise" (brisk walking to slow jogging) on platelet aggregation in a population-based sample of mildly hypertensive men in eastern Finland. In this controlled study, they evaluated the net effect of exercise on platelet aggregation by studying changes in optical density of platelet-rich plasma. A significant inhibition of secondary platelet aggregation, essentially reducing the body‟s ability to form clots, from 27% to 36% was observed in the men taking regular exercise. However,

these effects were studied in a white population of middle-aged subjects only, limiting the generalisability of these findings.

2.5.4: Anti-ischaemic effects

One of the main determinants of myocardial workload is increased blood pressure. Hypertension is another major risk factor for CVD which is influenced by exercise. Paffenbarger et al., (1983) presented the relationship between vigorous sports and blood pressure in almost 700 males graduating from Harvard who were followed up for 6-10 years. Presence or absence of a background of collegiate sports did not influence risk of hypertension in this study population, nor did stair-climbing, walking, or light sports play. However, alumni who did not engage in vigorous sports were at 35% greater risk of hypertension than those who did, and this relationship held at all ages, 35-74 years. Higher levels of body mass index, weight gain since college, history of parental hypertension, and lack of strenuous exercise independently predicted increased risk of hypertension in alumni.

A meta-analysis of 54 RCT‟s (2419 participants) whose intervention and control differed only in aerobic exercise, reported average reductions in systolic and diastolic blood pressure of 3.84 and 2.58 mmHg respectively (Whelton et al., 2002) thereby reducing myocardial demand. A further meta-analysis involved 72 trials, 105 study groups, and 3936 participants. After weighting for the number of trained participants and using a random-effects model, training induced significant net reductions of resting and daytime ambulatory blood pressure of, respectively, 3.0/2.4 mmHg ($P<0.001$) and 3.3/3.5 mmHg ($P<0.01$). The reduction of resting blood pressure was more pronounced in the 30 hypertensive study groups (-6.9/-4.9) than in the others (-1.9/-1.6); ($P<0.001$ for all) (Cornelissen & Fagard, 2005). This provides a compelling argument to include aerobic exercise in preventive cardiology practice where hypertension is common.

By reducing blood pressure, myocardial demand is also reduced. Aerobic exercise training also has been shown to improve myocardial oxygen supply by several mechanisms. These include extending the diastolic period of peak coronary flow by slowing the heart rate and by improving endothelial-induced vasodilatation of coronary resistance vessels by increasing NO synthesis and activity (Leon, 2009). In addition, moderate-intensity aerobic exercise improves arterial compliance, thereby reducing aging-related arterial stiffness (Seals et al., 2008). Furthermore, exercise training can increase the luminal area of conduit arteries by remodeling (arteriogenesis). In addition, animal studies have demonstrated exercise-induced increases in myocardial capillary density, analogous to

the angiogenesis demonstrated in skeletal muscle in both animals and humans (Duncker & Bache, 2008; Leon & Brown, 2012).

In summary, exercise improves the balance between myocardial oxygen demand and supply; it increases the maximal oxygen uptake of cells and coronary blood flow and, in being anti-ischaemic, it reduces heart rate and systolic blood pressure (hence reduced rate-pressure product). Consequently the oxygen demands during exercise and at rest decrease reducing the workload of the heart.

2.5.5: Anti-arrhythmic effects

Lethal ventricular tachyarrhythmias, often the initial presenting symptom of CHD, are responsible for a large proportion of CHD-related deaths in people older than 35 years of age (Leon, 2009). Vigorous physical exertion (>6 metabolic equivalent [MET] intensities) transiently increases risk of sudden cardiac death (SCD), as compared to risk at rest or during more moderate physical activity. Possible mechanisms include increased myocardial oxygen demands in the presence of narrowed coronary arteries, increased sympathetic activity or disruption of a vulnerable plaque. However, excess risk of SCD during vigorous activity is markedly lower in those who exercise regularly. This may be related to: a reduced rate-pressure product, improving coronary supply through extended diastole; direct cardiomyocyte adaptations, improving electrical stability of the heart; and reduced sympathetic and increased vagal stimulation of the heart. These latter training effects can be demonstrated by increased heart rate variability and a decrease in the sympathetic component of the heart rate–blood pressure baroreceptor response to stimuli following exercise training (Leon, 2009; Billman, 2002).

2.5.6: Summary

This section has highlighted some of the factors that may contribute to regular aerobic exercise and reduced incidence of myocardial infarction and increased longevity. As highlighted in a recent review, randomised controlled trial data supports the notion that exercise training induces a number of adaptive mechanisms in the blood, humoral and autonomic nervous system that are cardioprotective in nature (Golbidi & Laher, 2011). Collectively, this evidence provides strong support for a causal relationship between physical inactivity and CVD, and hence the role of exercise in preventing CVD. These same exercise induced adaptations benefit people who have survived a cardiac event e.g. myocardial infarction. Consequently aerobic exercise training is an established therapeutic intervention in preventive cardiology practice.

2.6: Exercise as therapy in secondary prevention

The previous sections have concentrated on the evidence base for physical activity and its role in protection from CVD. There is also a wealth of evidence indicating that activity and fitness are also important in people who are already afflicted by CVD. In contrast to the observational evidence from epidemiological studies concerning exercise and CVD prevention there is good evidence from randomised controlled trials confirming the effectiveness of exercise as a therapy for those who have clinical symptoms of CVD and for those who have survived a heart attack. The following will explore exercise as a therapy more closely in people with established CVD.

One area where exercise has been extensively studied in secondary prevention of cardiovascular disease is cardiac rehabilitation. The most recent Cochrane review and meta-analysis of exercise-based cardiac rehabilitation (CR) includes 10,794 patients from 47 randomised trials and reports an improvement in relative survival for those attending CR of 13% for all-cause mortality (relative risk (RR) 0.87, 95% CI 0.75 to 0.99) and 26% for cardiac mortality (RR 0.74, 95% CI 0.63 to 0.87) (Heran et al., 2011). These findings confirm those of the previously mentioned meta-analysis (Taylor et al., 2004). Despite inclusion of more recent trials, the population studied in this review were still predominantly male, middle aged and low risk. Therefore, well-designed, and adequately reported RCTs in groups of CHD patients more representative of usual clinical practice are still needed.

Further to mortality data, systematic review and meta-analysis by Lawler et al., (2011) of 34 randomised controlled trials (RCT) (6111 patients) showed that exercise-based CR attendees had a significantly lower risk of re-infarction (OR 0.53, 95% CI 0.38 to 0.76) than non-attendees. The findings of Davies et al., (2010a), Heran et al., (2011) and Lam et al., (2011) also suggest that the delivery of a comprehensive CR service has the potential to reduce unplanned cardiac readmissions by 28-56%. This has the potential to translate into sizable savings for the National Health Service. For example, a recent and powerful modelling exercise has shown the potential for the release of £30 million by increasing the uptake to CR by 15% (Kaiser et al., 2013).

Whilst the glue to cardiac rehabilitation is exercise, contemporary services include a comprehesive approach (Buckley et al., 2013). The intervention used in the EUROACTION study mimicks that of modern cardiac rehabitation but applies it to a broader patient population. In evaluating evidence for a multifactorial approach to cardiac rehabilitation as opposed to exercise-based rehabilitation, the Global Secondary Prevention Strategies to Limit Event Recurrence After MI (GOSPEL) trial (Giannuzzi et al., 2008; Giannuzzi et al., 2005) persuasively defined the impact of a multidisciplinary programme on lifestyle behaviours (including physical activity), risk factors management and use of cardioprotective drug therapies in patients with CHD. The GOSPEL study also assessed the impact of such a programme on major cardiovascular events. This randomised trial was carried out in 78 Italian cardiac rehabilitation centres investigating the efficacy of long-term, reinforced, multifactorial educational and behavioural intervention versus usual care after MI.

GOSPEL enrolled patients with recent MI (<3 months) routinely referred to a cardiac rehabilitation centre. All patients completed a standard CR program lasting approximately 1 month and consisting of supervised exercise sessions and comprehensive lifestyle and risk-factor management along with optimisation of medical therapy. After completion of the standard CR programme, the patients were randomised to either receive an intensive, 3-year long, multifactorial intervention or be monitored for usual care. Comprehensive CR sessions with one-to-one support were held monthly from month 1 to month 6, then every 6 months for 3 years.

Their intervention programme significantly improved adherence to these lifestyle behaviours and prescribed medications, which importantly translated to a reduction in major cardiovascular events. At 6 months, the difference in the level of physical activity from baseline between the two groups was higher in the intervention group and it was maintained throughout the study (23.8 vs 18.8%; $p = 0.01$). Whilst these GOSPEL results are encouraging, it is shocking that more than three quarters of the intervention group, despite an intensive intervention were not sufficiently active. In usual care, despite receiving a standard cardiac rehabilitation programme, the prevalence of inactivity was even worse.

Exercise has been shown to be more effective than some surgical techniques for treating CVD. One example is a randomised controlled trial of exercise training versus revascularisation through surgical percutaneous coronary intervention (PCI) in 101 males, aged less than 70 years, with stable coronary artery disease. Those assigned to the exercise intervention participated in 20 minutes of cycling per day for 12 months. Maximum oxygen uptake increased by 16% in the exercise training group while remaining unchanged in those that underwent surgery. Exercise training was associated

with a higher event free survival than PCI (88% versus 70% respectively; P=0.023) and was cheaper. Cost efficiency was calculated as the average expense (in US dollars) needed to improve the Canadian Cardiovascular Society class by 1 class. For the PCI group this equated to $6956 versus $3429 dollars in the training group (P<0.001) (Hambrecht et al., 2004).

The mechanisms by which exercise improves outcomes for people with CVD are uncertain but are thought to involve improved myocardial perfusion and endothelial function as described earlier. There is also the suggestion that coronary atherosclerosis is to a small but important degree reversible. The Lifestyle Heart Trial demonstrated that intensive lifestyle changes may lead to regression of coronary atherosclerosis after 1 year (Ornish et al., 1998). Forty-eight patients with moderate to severe coronary heart disease were randomised to an intensive lifestyle change group or to a usual-care control group. Intensive lifestyle changes included a strict diet (10% fat intake and vegetarian), aerobic exercise, stress management training, smoking cessation, group psychosocial support initially for 1 year but the trial was then extended to 5 years. At 1 year and at 5 years subjects were followed up with quantitative coronary arteriography – a gold standard measure for assessment of the degree of coronary stenosis.

In the experimental group, the average percent diameter stenosis at baseline decreased 1.75 absolute percentage points after 1 year (a 4.5% relative improvement) and by 3.1 absolute percentage points after 5 years (a 7.9% relative improvement). In contrast, the average percent diameter stenosis in the control group increased by 2.3 percentage points after 1 year (a 5.4% relative worsening) and by 11.8 percentage points after 5 years (a 27.7% relative worsening) (P=.001 between groups). However, in interpreting the results it is important to note there was more than a 25% drop out and these findings were based on 71% (20 patients) and 75% (15 patients) completing the 5 year follow-up in the intervention and control groups respectively.

Whilst a small trial with notable drop-out and consequently limited feasibility to implement more widely, these findings are highly motivating for programmes centred on healthy lifestyle behaviours as it shows the effects of making and sustaining lifestyle changes, without the use of lipid lowering drugs, on coronary heart disease. The exact contribution of the exercise itself is less clear. Exercise frequency and duration overall was considerably higher at 1 year with modest adherence at 5 years in the intervention group. Although these differences in activity dose were not statistically significant the sample size was small and the limitations of self-reported activity should be also noted.

Current national clinical guidelines and quality standards (NICE CG48, NICE CG94, NICE CG108 and NICE QS9) which recommend CR for specific cardiac conditions and treatments are based on a wealth of research evidence demonstrating the positive outcomes of CR. However in 2012, the efficacy of cardiac rehabilitation in the UK was challenged. A multi-centre randomised controlled trial in representative hospitals in England and Wales, entitled Rehabilitation After Myocardial Infarction (RAMIT), compared 1813 patients referred to comprehensive cardiac rehabilitation programmes or discharged to 'usual care' (without referral to rehabilitation). The primary outcome measure was all-cause mortality at 2 years. The secondary measures were morbidity, health service use, health-related quality of life, psychological general well-being and lifestyle cardiovascular risk factors at 1 year. Patient entry ran from 1997 to 2000, follow-up of secondary outcomes to 2001 and of vital status to 2006 (West et al., 2012).

There were no significant differences between patients referred to rehabilitation and controls in mortality at 2 years (RR 0.98, 95% CI 0.74 to 1.30) or after 7-9 years (0.99, 95% CI 0.85 to 1.15), cardiac events, seven of eight domains of the health-related quality of life scale ('Short Form 36', SF36) or the psychological general well-being scale. Rehabilitation patients reported slightly less physical activity. No differences between groups were reported in perceived overall quality of cardiac aftercare (West et al., 2012). This trial was however stopped prematurely and was considerably underpowered. Whilst the participating centres may not necessarily be representative, the lack of any effect size raises serious doubts as to the value of CR as practised in the UK. However, in reviewing the exercise volume and dose delivered by the centres included in the RAMIT trial there was a total of 7 hours on average of moderate intensity supervised exercise. This falls far short of that associated with the latest Cochrane reviews findings on the amount of exercise needed to be effective and consequently it is unsurprising that cardiac rehabilitation was found to be ineffective.

Further work has highlighted that CR programmes in the UK are not delivering the volume or dose of exercise intervention associated with the evidence-base. Sandercock et al., (2013) recently quantified prescribed exercise volume and changes in cardiorespiratory fitness in UK cardiac rehabilitation patients. They accessed 950 patients who completed cardiac rehabilitation at four UK centres and extracted clinical data and details of cardiorespiratory fitness testing pre- and post-rehabilitation. Patients completed 6 to 16 (median 8) supervised exercise sessions. Effect sizes for changes in fitness were d=0.34-0.99 in test-specific raw units and d=0.34-0.96 expressed as METs. The pooled fixed effect estimate for change in fitness was 0.52 METs (95% CI 0.51 to 0.53); or an effect size of d=0.59 (95% CI 0.58 to 0.60). Gains in fitness varied by centre and fitness

assessment protocol but the overall increase in fitness (0.52 METs) was only a third the mean estimate reported in a recent systematic review (1.55 METs) (Heran et al., 2011). If representative of UK services, these low training volumes and small increases in cardiorespiratory fitness may partially explain the reported inefficacy of UK cardiac rehabilitation to reduce patient mortality and morbidity.

In summary, as cited in a recent editorial, the evidence for CR has been extensively reviewed by the National Institute for Health and Clinical Excellence, the American Heart Association, the American College of Cardiology, the World Health Organisation and many other bodies, all of whom have recommended its numerous benefits. These include increased exercise capacity, improved quality of life and health behaviours and a reduction in cases of anxiety and depression.

There is no doubt that high quality CR saves lives and improves quality of life but to be effective interventions, including the exercise intervention, must be delivered at the intensity associated with this evidence-base. In addition, patients need to participate in order to realise these benefits. Of concern, the National Audit of Cardiac Rehabilitation continues to highlight that, year on year, the average uptake among the main treatment groups in England remains below 50% (National Audit of Cardiac Rehabilitation, 2012). This highlights the need for services to not only evolve their practice to deliver the right dose of intervention but also explore effective ways to address the barriers and increase uptake.

2.7: Interventions to increase participation in centre-based exercise programmes

There are established guidelines as to the content of an effective intervention designed to increase physical activity participation and also induce gains in cardiorespiratory fitness (ACPICR, 2009). However, in order to realise these benefits one has to take part. As part of designing an effective centre-based intervention to increase physical activity participation and cardiorespiratory fitness it is essential to consider methods that will engage people affected by CVD (or who are at high risk of developing disease) to attend and participate in the physical activity intervention in the very first instance. Given that preventive cardiology is essentially a model of cardiac rehabilitation applied to a broader population, a review of literature pertaining to this area will be the main focus. The purpose of this section of the review is to explain in brief the rationale for including specific interventions as part of the design of the physical activity and exercise protocol used in the EUROACTION study.

2.7.1: Early programme initiation

Evidence would suggest that there are considerable benefits in relation to increased participation by ensuring programme commencement occurs within 10 days of referral. Consequently this is recommended by the National Institute for Health and Care Excellence (NICE, 2013). At the time of referring to a preventive cardiology programme, people have either just been diagnosed with cardiovascular disease or advised that they are at high risk of having a heart attack or stroke in the next five to ten years. This is a time when people are particularly reception and therefore avoiding delays is critically important.

In the UK, the last NACR report highlighted a mean delay of 56 days to commence an outpatient cardiac rehabilitation programme (National Audit of Cardiac Rehabilitation, 2012), which may in part explain the low average uptake of 46%. An early appointment to outpatient cardiac rehabilitation at hospital discharge has been shown to significantly improve attendance in a randomised, single-blind, controlled trial (Pack et al., 2013b). In this comparison 148 patients with a nonsurgical qualifying diagnosis for CR were randomised to receive a CR orientation appointment either within 10 days (early) or at 35 days (standard). The primary end point was attendance at CR orientation. Unlike many other studies in CR there was a good balance in sex and ethnicity; 56% of participants were male and 49% were black, with balanced baseline characteristics between groups. Median time (95% confidence interval) to orientation was 8.5 (7-13) versus 42 (35 to NA [not applicable]) days for the early and standard appointment groups, respectively ($P<0.001$). Attendance rates at the orientation session were 77% (57/74) versus 59% (44/74) in the early and standard appointment groups, respectively, which demonstrates a significant 18% absolute and 56% relative improvement (relative risk, 1.56; 95% confidence interval, 1.03-2.37; $P=0.022$). This simple technique could potentially increase participation in cardiovascular prevention and rehabilitation programmes nationwide.

2.7.2: Motivational invitation techniques

Davies et al., (2010) searched a wide variety of databases and found ten randomised controlled trials that were suitable for inclusion (three trials of interventions to improve uptake, and seven of interventions to improve adherence). The studies evaluated a variety of techniques to improve uptake or adherence and in many studies a combination of strategies was employed. The quality of studies was generally low. All three interventions targeting uptake of cardiac rehabilitation were effective. Two of seven studies intended to increase adherence to exercise as part of cardiac rehabilitation had a significant effect (one of which was of poor quality).

The interventions evaluated included motivational letters (Wyer 2001), motivational telephone contact (Hillebrand 1995) and co-ordination of care by a trained nurse, together with patient self monitoring of contact with health professionals (Jolly 1999). The multifaceted nature of the latter trial meant that it was not possible to identify which were the active components of the intervention that brought about the increase in uptake.

Hence it would seem there are advantages to planning the EUROACTION physical activity intervention to include motivational approaches in terms of the invitation letter and scheduled telephone contact.

2.7.3: Goal setting, action planning and contractual agreements

In the most recent review by Davies et al., (2010) seven studies of interventions to improve adherence were identified. A wide variety of techniques, and combinations of techniques, were evaluated including goal setting, action planning, self-monitoring (of exercise, daily activities, body weight, heart rate, smoking, and contact with health professionals), feedback, problem-solving and coping strategies, written and oral commitment, stress management, persuasive written and telephone communication, and small group interaction and peer modelling.

The majority of studies found no significant effect of the interventions on adherence. Two studies found significant effects (Duncan & Pozehl, 2002; Sniehotta et al., 2006) of unsupervised exercise in patients who had previously completed a programme of supervised exercise. It should be noted though that the follow up period for both of these two studies was less than 12 weeks.

The former trial investigated the effectiveness of an adherence facilitation intervention consisting of goal setting, graphic feedback, and provider guidance to support adherence to home exercise in a sample of patients with heart failure. The sample consisted of 13 patients with an ejection fraction of 40% or less who were randomly assigned to either the exercise only group (n=6) or the exercise with adherence facilitation group (n=7). Results indicate that patients who received the intervention demonstrated higher exercise adherence and greater confidence in continuing to exercise in the future (Duncan & Pozehl, 2002). However, the study sample was very small and the risk of bias was difficult to assess due to a lack of information in the study report.

Sniehotta et al., (2006) found that developing coping plans to overcome anticipated barriers together with action plans was more effective than action planning alone or usual care. Action planning alone was not more effective than usual care, suggesting that coping plans were the most important component in the combined intervention. However, randomisation was achieved by alternate allocation, which is a weak method. Adherence to exercise was self-reported and there was no information within the study report about whether those assessing outcomes were blind to the participants‟ treatment allocations. These factors may have introduced bias into the results of the study.

2.7.4: Summary

In summary, there is a wealth of data reporting on the barriers to cardiovascular prevention and rehabilitation programmes and possible interventions to address these. However, much of the research is of poor quality with few studies including any blinding and little consistency in the definition of adherence. Furthermore, few studies reported the effects of the interventions on clinical outcomes or health related quality of life and none provided information about costs or resource implications. The differences between the strategies used in the studies identified mean that it is difficult to make clear recommendations. Following a review of the evidence a summary of strategies that may increase uptake and programme completion is provided in Figure 2.7.1. In designing an effective preventive cardiology programme these should be considered. However, further high quality research is needed.

Figure 2.7.1: Summary of interventions to increase uptake and adherence to exercise-based cardiac rehabilitation

Interventions to increase uptake	Interventions to increase adherence
▪ Motivational letters* ▪ Motivational telephone contact* ▪ Home visits* ▪ Co-ordination of care by a trained nurse* ▪ Automatic referral systems* ▪ Inpatient visit by cardiac rehabilitation liaison* ▪ Early programme orientation (<10 days)* ▪ Use of lay volunteers ▪ Offering choice ▪ Provide transport ▪ Care for dependents	▪ Planning and goal setting* ▪ Signed commitment or diary* ▪ Gender tailored programmes* ▪ Early programme orientation*

**Supported by RCT data.*

2.8: Why include partners in the exercise intervention?

In addition to the above, it is proposed the active inclusion of the patient‟s spouse within a structured programme of care can positively influence outcomes. The justification is in part because evidence suggests „like marries like‟ and consequently CVD risk factors are shared (Wood et al., 2004). Hence in treating a patient affected by cardiovascular disease this also provides an opportunity to apply primary prevention to a household more widely. Additionally, involving the spouse will support the lifestyle changes required to achieve cardiovascular health more effectively. In terms of physical activity, it is not uncommon for family members to discourage activity in their loved one following a cardiac event for fear of inducing a further episode. Hence, a couple taking part in the exercise intervention together can alleviate these fears (Moser and Dracup, 2004).

Various theories have been put forward to explain reasons for concordance in couples and for the mechanisms for partners influencing each other‟s health behaviours (Zietsch et al., 2011; Umberson, 1987; Epstein & Guttman, 1984). The theory that appears to have most support in the concordant literature is that of „non-random mating‟ although the mechanisms for this are not entirely understood (Zietsch et al., 2011; Watson et al., 2004). Non-random mating can occur in one of two ways. Individuals may select a mate on the basis of a particular phenotype, e.g. exercise, or because of social homogamy. Alternatively, the explanation for concordance may be convergence in behaviours over the duration of a relationship. When partners marry, they share the same social and home environment and available finances (Smith & Zick, 1994). Another important mechanism, particularly in relation to concordance for health behaviours, is social control. This is exerted when one spouse tries to control the behaviours of the other, and is usually the female partner (Umberson, 1987). Women, more than men, take responsibility for the organisation of the home environment, for example in buying and preparing food. They also take responsibility for maintaining the health of their husbands, possibly by persuading him to exercise (or not) if he has experienced a health problem.

2.9: Closing remarks

Cardiovascular disease remains the leading cause of death in Europe and Worldwide. Adverse trends in obesity and diabetes indicate a looming global epidemic of people living with cardiovascular disease. The United Nations recognise the importance of this issue, instigating a declaration for the World to come together in a concerted effort to prioritise prevention and reduce cardiovascular disease by 25% by the year 2025.

There is a wealth of epidemiological evidence that consistently supports the role of physical activity and cardiorespiratory fitness in the prevention and management of cardiovascular disease. Randomised controlled trial data is lacking but it is practically impossible (and unethical) to randomise people to sedentary living and then follow them up for events. Establishing a causal relationship in a double blind randomised controlled trial in primary prevention is therefore unrealistic. However, there are many studies (and in the most part RCT‟s) to explain the underpinning cardioprotective mechanisms of exercise training, thereby suggesting that a causal pathway exists between participation in exercise training and protection from CVD. Given these, together with consistent observational findings, physical inactivity and low fitness are both established independent risk factors for CVD. Hence, exercise training and encouraging active living should be important components of any preventive cardiology programme as well as more widely in the context of reducing the global burden of cardiovascular disease.

In people who have established atherosclerosis, e.g. in those with coronary heart disease, the evidence base for exercise training and lowered risk of mortality is strong. There are several meta-analyses (the latest involving almost 50 RCT‟s) reporting significant reductions in all-cause mortality, lowered cardiac mortality and improved quality of life. However, there is evidence to suggest that in cardiac rehabilitation the overall dose of exercise interventions delivered in the UK is far from optimal and not in accordance with that reported in these clinically effective trials. It is essential when designing the exercise intervention for a preventive cardiology programme that the frequency, intensity, duration and type of activity are all fully considered and an evidence-base dose is applied if the benefits are to be realised.

Despite these benefits, cardiovascular prevention and rehabilitation programmes remain considerably underutilised. In the UK, less than half of eligible patients avail of cardiac rehabilitation; essentially a lifesaving intervention. If exercise interventions are to be of any benefit they need to employ strategies to engage people to participate in the first instance. Whilst some

interventions have been shown to be effective at increasing uptake and adherence (such as early programme commencement and motivational invitation letters) further high quality research in this area is required.

Finally, physical activity is multidimensional and therefore challenging to measure as no single method can capture all subcomponents and domains. The perfect assessment method does not exist and accordingly selection of methods must be based on careful consideration of the pros and cons, indications for use and the evidence to support it. Preventive cardiology programmes are often community-based and the choice of methods may therefore be a compromise between accuracy level and feasibility.

Given this review and the evidence presented, the methodology that follows will incorporate:

- Feasible measures to assess both physical activity and cardiorespiratory fitness;
- A physical activity and exercise intervention designed to increase uptake and programme completion;
- An activity and exercise intervention that aims to achieve the doses associated with reduced mortality, reduced morbidity and increased quality of life;
- The inclusion of partners in the physical activity and exercise intervention, wherever possible.

Chapter 3:

Methodology

3.1*:* *EPAF- Study objectives*

3.2*:* *EPAF-Study design*

3.3: *EPAF-Study settings*

3.4: *EPAF-Study population*

3.5: *Ethical procedures*

3.6 *Personnel and training*

3.7: *Outcome measures*

3.8 *Assessment time points*

3.9 *Statistical methods*

3.10: *Assessment methodology*

3.11 *The physical activity and exercise intervention*

3.12 *Quality assurance*

3.13: *Summary*

As presented in Chapter 2, the scientific evidence for cardiovascular disease (CVD) prevention is compelling; it shows that lifestyle intervention, risk factor management, and cardioprotective drugs can reduce cardiovascular morbidity and mortality in patients with established atherosclerotic disease and those at high risk of developing the disease (Graham et al., 2007). However, results of risk factor management in patients with coronary heart disease in the European Action on Secondary and Primary prevention through Intervention to Reduce Events (EUROASPIRE) surveys showed that CVD prevention in routine clinical practice has remained inadequate in each of the four surveys to date (Kotseva et al., 2010; Kotseva et al., 2009a; Kotseva et al., 2009b; EUROASPIRE II Study Group, 2001; EUROASPIRE Study Group, 1997).

As the foreword details, the EUROACTION study was conceived in recognition that this gap between recommendations and daily practice is substantial and set out to demonstrate if a preventive cardiology programme could better help patients with coronary heart disease, high multifactorial risk, and diabetes outside specialist cardiac rehabilitation centres to effectively achieve the lifestyle, risk factor, and therapeutic targets defined in the prevention guidelines in routine clinical practice. The effectiveness of the addition of a preventive cardiology programme, entitled EUROACTION, comprising of a nurse-led multi-disciplinary team approach, coupled with the support of a patient‟s partner and family was tested in a cluster randomised controlled trial. The methodology and the main findings of the EUROACTION study have been previously published (Appendices 1 and 2).

This chapter describes the methodology for a further study entitled the EUROACTION Physical Activity and Fitness Study (EPAF-Study), which was nested within the trial. As the EPAF-Study was "a study within a study" some parameters were consequently predetermined including; the study population, sample size and research settings. The EPAF-Study objectives conversely were unique and focus on the topic of physical activity in clinical preventive cardiology settings. Chapter 2 provides this rationale by highlighting that physical inactivity is responsible for up to 9% of all premature mortality worldwide (Lee et al., 2012) and is the fourth leading risk factor for mortality (World Health Organisation, 2009). The current levels of physical activity in Europe are considerably low and emphasise the urgent need to discover solutions that achieve meaningful gains in activity as part of addressing the growing burden of cardiovascular disease in Europe. The EPAF-Study set out to determine if the EUROACTION model could more effectively increase physical activity participation and

cardiorespiratory fitness in Europe compared to what is currently being achieved in clinical practice.

3.1: EPAF-Study objectives

The EUROACTION trial was found to better increase *subjectively measured* physical activity participation than routine clinical practice in hospital centres and general practices, at a European level (Wood et al., 2008; Appendix 2). The aim of this study was to evaluate the impact of the EUROACTION programme on *objectively measured* physical activity participation and on cardiorespiratory fitness in order to more rigorously assess if this model of care achieves more than current usual care.

There are two parts to this study - an evaluation of a hospital-based programme and another based in general practice. Whilst the underpinning philosophy and the overall goals are shared their study populations and the design of their interventions differed.

The study objectives for the **HOSPITAL** component:

Primary objective:

To evaluate the impact *at 1-year* of a ***16-week physiotherapy-led physical activity and supervised exercise intervention*** on *objective physical activity participation* and *cardiorespiratory fitness* in ***coronary patients*** compared to usual care.

Secondary objective:

To evaluate the change in *physical activity participation* and *cardiorespiratory fitness* between baseline and 16-weeks in coronary patients randomised to the EUROACTION intervention.

The study objectives for the **GENERAL PRACTICE** component:

Primary objective:

To evaluate the impact *at 1-year* of a ***1-year nurse-led physical activity intervention*** on *objective physical activity participation* and *cardiorespiratory fitness* in ***high risk patients*** compared to usual care.

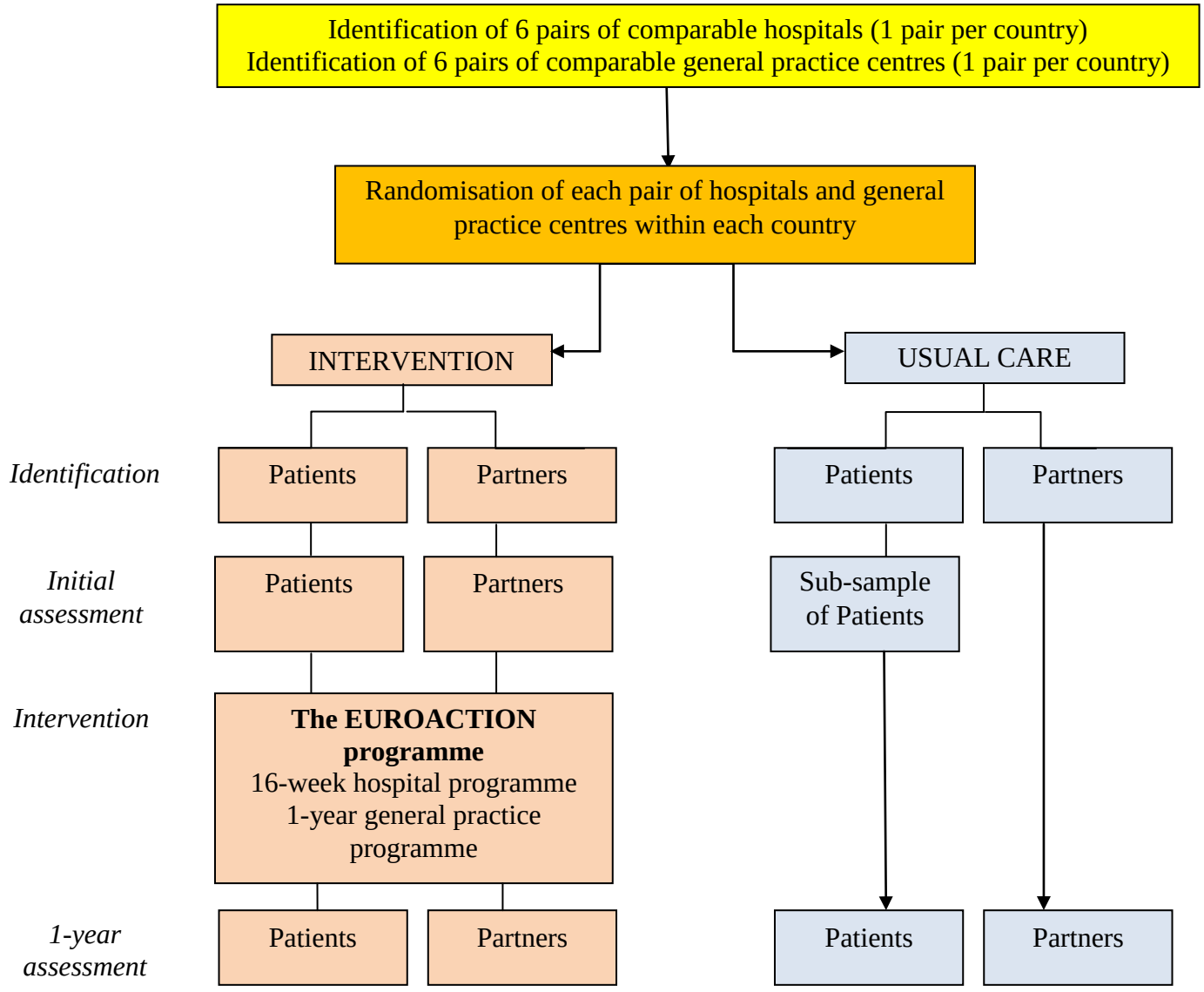
Secondary objective:

To evaluate changes in *physical activity participation* and *cardiorespiratory fitness* from the initial assessment to 1-year in high risk patients randomised to the EUROACTION programme and usual care.

3.2: EPAF-Study design

The design of this study was predetermined as it was a sub-study within the EUROACTION trial, which has been previously published (Wood et al., 2008; Appendices 1 & 2). By way of a short introduction, EUROACTION was a matched, paired cluster-randomised controlled trial with clinical follow up at 1 year (Figure 3.2.1).

Figure 3.2.1: EUROACTION Cluster Randomised Controlled Study design



3.3: EPAF-Study setting

The settings were also pre-determined by the collective efforts of the steering group (which the author was a member of). The centres selected were busy district general hospitals and practices, and not academic teaching centres. In this way, the aim was to show that this preventive cardiology care model offers equitable access to patients and their families in their own localities and is applicable and generalisable to every day clinical practice. The EUROACTION trial was done in 12 (six pairs) of general hospitals in France, Italy, Poland, Spain, Sweden, and the UK, and 12 (six pairs) of general practice centres in Denmark, Italy, Poland, Spain, the Netherlands, and the UK (Appendix 5).

3.4: EPAF-Study population

The study population for the EPAF-Study was also defined by the EUROACTION study steering group, which included the author. For this study the same inclusion and exclusion criteria applied. The hospital part of the study recruited coronary patients and their families. The nurse identified consecutive patients (men and women) less than 80 years of age with a first presentation of coronary artery disease in the following diagnostic categories:

1. Acute myocardial infarction (AMI)
2. Unstable angina (UA)
3. Stable (exertional) angina (SA)

Patients in general practice were between 50 and 80 years of age with no history of cardiovascular disease but identified as people at high risk of developing cardiovascular disease in the next 10 years. Patients were either newly identified through a calculation of their "HeartScore" or they presented with known CVD risk factors that were currently under medical therapies. In relation to the former, HeartScore is an established risk estimation tool developed by the European Society of Cardiology (Conroy et al., 2003) which quantifies cardiovascular risk based on age, sex, smoking status, blood pressure and cholesterol. A score greater than five percent represents "high risk" of mortality from CVD events over the next 10-years. To recruit the general practice population, the nurse identified consecutive patients (men and women), who had been identified as being at high risk of developing cardiovascular disease. Each high risk patient was categorised and allocated to one of three groups:

1. Group I - HeartScore >5%: Men with at least 1 (women with at least 2) untreated cardiovascular risk factor(s), (smoking and/or raised blood pressure [≥140/90 mmHg] and/or raised total cholesterol [≥ 5 mmol/l]), who had a total CVD risk according to the European HeartScore charts of ≥ 5% for cardiovascular mortality over 10 years, either currently or when projected to age 60 years (Conroy et al., 2003).
2. Group II- Patients on treatment for hypertension and/or hypercholesterolemia: Men or women started on treatment in the last year with antihypertensive and/or lipid-lowering therapies but with no history of diabetes.
3. Group III – Known diabetes: Men or women diagnosed in the last 3 years with diabetes and on treatment with diet, oral hypoglycaemics and/or insulin regardless of concurrent treatment for hypertension and/or dyslipidaemia.

Exclusion criteria for all patients in the hospitals and general-practice centres (beyond age and diagnosis) were severe heart failure, severe physical disability, or dementia. Severe heart failure, pertaining to New York Heart Association grade four (NYHA IV) and palliative care, where attendance at a weekly cardiovascular health programme would not be appropriate. Those with severe physical disability were defined as those wheelchair-bound; essentially excluded as they would be unable to participate in the structured activity programme which involved the ability to stand. Finally those with dementia were excluded as the programme involved a large-degree of development of self-management strategies and the ability to achieve this would be considerably compromised without sufficient cognitive function.

3.5: Ethical procedures

The ethical procedures were dealt with collectively by the central coordinating group, which included the author. Local Research Ethics Committees approval at each centre was required before the study could start and this was ultimately the responsibility of each of the 8 national coordinators. Written informed consent was obtained from all patients and their partners (Appendix 6). Given that all individuals received the care available to them within their cluster i.e. usual care or in intervention clusters‟ the EUROACTION programme, they were essentially consenting to allow their data to be included. The trial was also registered (Trial Registration Number: ISRCTN71715857).

3.6: Study personnel and training

The author was solely responsible for the recruitment of six experienced physiotherapists with appropriate knowledge and skills to lead the physical activity and exercise intervention in the EUROACTION hospital intervention centres. This required developing job descriptions and working closely with the principle investigator from each of the intervention centres to translate recruitment materials and assist with advertisement and the subsequent interviews for the positions. For the nurse positions, either as a usual care nurse or an intervention nurse in general practice, the author supported the nurse coordinator from the central team accordingly in the recruitment of appropriately skilled personnel for the study.

Three training meetings, each lasting a week, were held in London which brought together the teams from across the eight countries. The multiple languages meant full translation of training materials as well as the use of interpreters, translator booths and numerous language channels. All individuals also received a fully translated *Health Professional Manual* (intervention or usual care version as relevant) that essentially covered the study protocol in detail. The author singly developed and delivered the training programme in relation to the physical activity and exercise component. She also took full responsibility for developing the content of the *Health Professional Manual* with regards to this same topic, together with overseeing and validating its translation. An established and experienced agency was recruited to provide all interpreters and translation services. All written materials were translated into each of the languages, reviewed by the steering group members and then back-translated into English. All translations were performed by medical translators using human as opposed to machine translation.

In ensuring to maximise both fidelity and transparency in translation the steering group were involved. Each country was represented by a national coordinator and each intervention and usual care centre by a principle investigator. For the seven countries besides the United Kingdom these individuals were all English literate. Each of these individual‟s was required to review the translated versions for their country and identify amendments. In the mainstay these related to ensuring the translations conformed to grammar, syntax and idiom for the language concerned. The medical translators then back-translated these and the central team, including the author, were required to evaluate their fidelity.

3.7: Outcome measures

The EUROACTION study has previously published its methodology and findings in relation to the primary end point for physical activity (Appendices 1 & 2). This was determined by categorising the achievement (or not) of the European Guidelines for Physical Activity (EGPA) (Graham et al., 2007) via a seven day activity recall (7-DAR). Essentially this represents a subjective measurement of physical activity.

For the EPAF-Study, the physiotherapists and nurses, where applicable, were trained to assess physical activity participation using an objective measurement tool. Whilst an accelerometer would have been the preferred measurement tool this was not economically feasible and therefore a pedometer was selected. The outcome measures for physical activity participation were two continuous variables (mean steps per day and proportion of patients achieving greater than 10,000 steps per day on average) and a categorical measure using Tutor Locke"s Categorisation (2004) (Figure 2.4.2). The latter threshold was selected as this is the recognised target within the European physical activity guidelines (Graham et al., 2007).

All three of these outcomes were determined by wearing a Yamax Digiwalker SW-200 pedometer for seven consecutive days. This particular model was selected in recognition that it was found, and remains to a large extent, to most consistently accurately measure steps per day under both controlled and free-living conditions (Butte et al., 2012; Le Masurier et al., 2004; Schneider et al., 2004; Schneider et al., 2003; Welk et al., 2000).

The outcome measure for cardiorespiratory fitness was mean metres scored in the Incremental Shuttle Walk Test (ISWT) (Singh et al., 1992) in coronary patients (hospital study) and time achieved in the Chester Step Test (CST) (Sykes, 1998) in asymptomatic individuals at high risk of heart attack or stroke in the next five to ten years (general practice study). The ISWT was selected for the coronary patients as there is systematic review evidence to support it as a valid and reliable measure of peak oxygen uptake in this population (Parreira et al., 2014). Conversely, the ISWT has not been validated in the apparently well population. In the knowledge of this, coupled with the very limited space available in the general practice settings, the CST was selected as the method of choice to determine cardiorespiratory fitness in the population found to be at high risk of developing CVD.

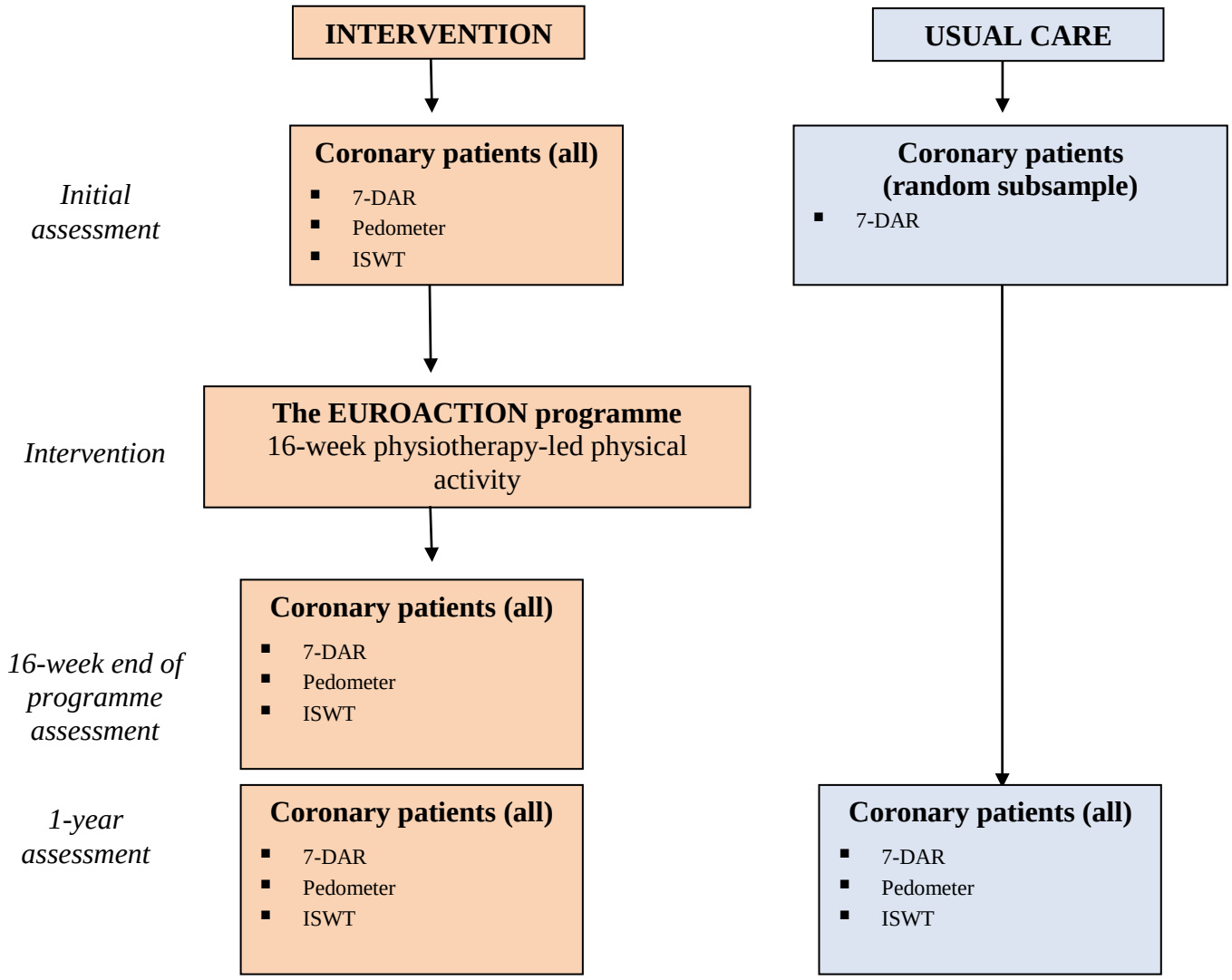
Whilst there are no systematic reviews of the CST available to date, findings from single prospective cohort studies indicate that this test is appropriate and reliable for the assessment of aerobic capacity in the apparently well and those at CVD risk in a clinical setting (Stevens & Sykes, 1996; Buckley et al., 2004; Cooney et al., 2013).

3.8: Assessment time points

There are important distinctions in the assessment time points for the hospital and general practice parts to this study that the reader should note. The hospital study preceded that in general practice. The assessment at baseline in its entirety was very long for the hospital study; lasting over 3-4 hours per participant. Consequently, it was not appropriate to add further measures to the initial assessment in usual care. The additional time was likely to impact on attendance and also willingness to re-attend at 1-year. In the EPAF-Study all patients in the hospital *intervention* group were assessed at three time points – the initial assessment, at the end of the intervention programme at 16-weeks and again at the final assessment at 1-year. All those in the *usual care* group participated only once (at the 1-year assessment) (Figure 3.8.1a). Therefore the EPAF-Study was only able to evaluate the effect of the intervention over time in the treatment (i.e. intervention) group. The impact of the programme overall compared to usual care could only be evaluated by a comparison at 1 year.

In the general practice study the initial assessment for the main study was much shorter (lasting 1.5 – 2 hours on average). It was therefore possible to improve on the methodology in this second study and include additional physical activity parameters at the baseline assessment in usual care. In the general practice study step data was collected in the entire intervention group and a random subsample of the usual care group at baseline and then in all participants at 1-year. Fitness data was collected at baseline in a random subsample in both intervention and usual care and then in all participants at 1-year (Figure 3.8.1b).

Figure 3.8.1a: Time points and measures of physical activity participation and cardiorespiratory fitness (hospital study)

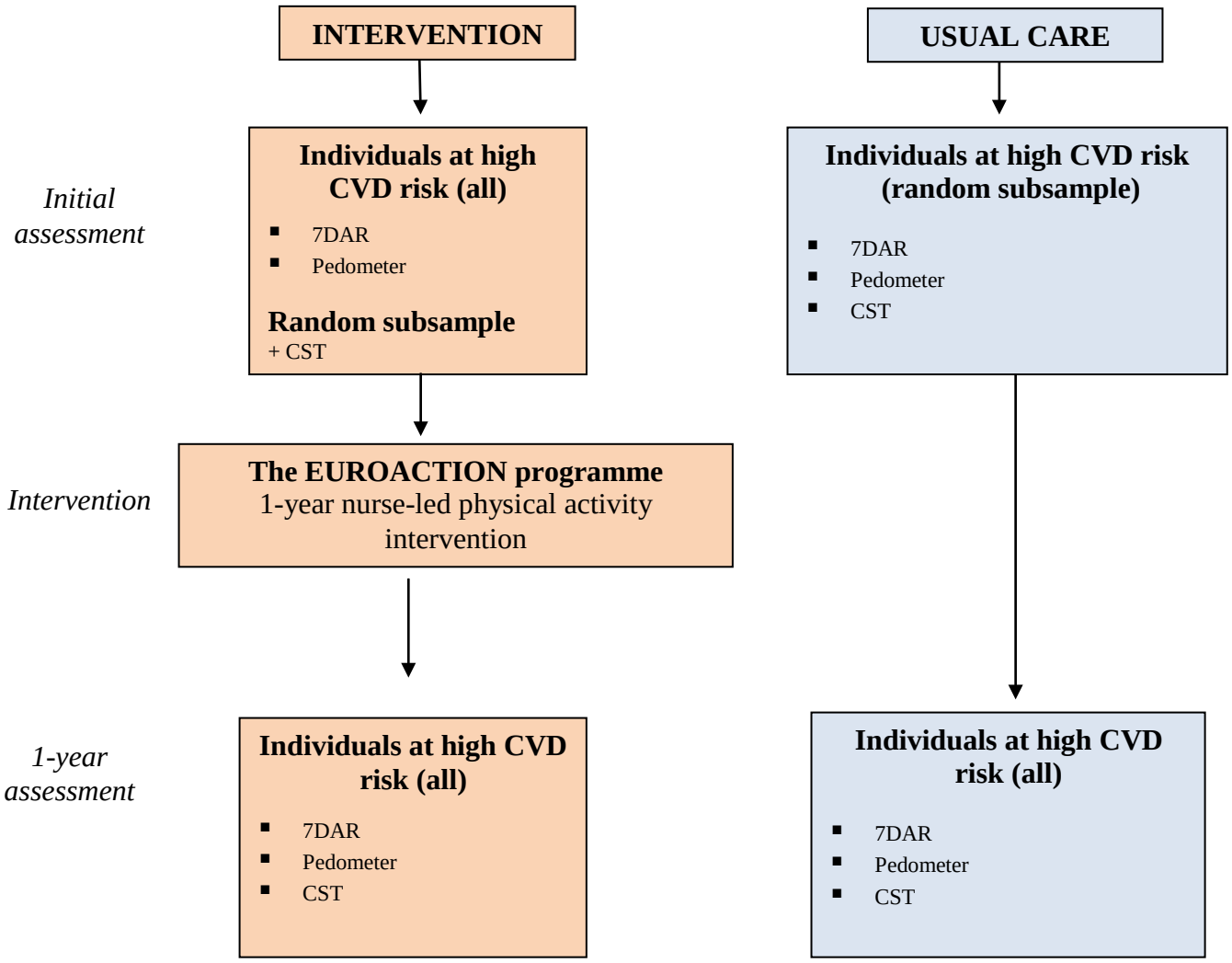


Key:

7-DAR = seven day activity recall
ISWT = Incremental Shuttle Walk Test (a 12-stage submaximal walking based test with fixed workloads (set by audio bleeps) with increments every minute)

The identification of patients allocated to the random subsample was computer generated. The selection of a random subsample of usual care (as opposed to all) for the assessment at baseline was purposefully employed in recognition that the assessment in itself could act as an intervention. By including this random subsample at baseline, it provided the added advantage of being able to evaluate the difference in the change over time in physical activity participation and cardiorespiratory fitness between the general practices receiving the intervention and those being monitored for usual care.

Figure 3.8.1b: Time points and measures of physical activity participation and cardiorespiratory fitness (general practice study)



Key:

CVD = cardiovascular disease.
7-DAR = seven day activity recall (self-reported activity lasting more than ten minutes continuously for the seven days leading up to the assessment.
CST = Chester Step Test (a 5-stage submaximal stepping test with fixed workloads (set by audio bleeps) with increments every two minutes).

3.9: Statistical methods

The main study was powered for a European level analysis (Appendix 2) and the analyses for this study purposefully mirrored this approach in order to provide a more rigorous evaluation of the programme and draw conclusions in a standardised way.

All analyses were made on an intention-to-treat basis with patients being invited back to the final assessment irrespective of whether or not they attended the EUROACTION programme. Six intervention hospitals were compared with six usual care hospitals, and six intervention general practices were compared with six usual-care practices at 1 year. To account for clustering, the primary endpoints for this study were analysed with random-effects modelling (with restricted maximum likelihood estimation) using SAS PROC MIXED (version 9.1.3) for continuous outcomes (mean steps per day, metres scored in the ISWT and time achieved in the CST) and SAS GLIMMIX (version 9.1.3) for binary outcomes (proportion achieving more than 10,000 steps per day). For the ordered categorical outcome (Tudor-Locke step categorisation), proportional odds models were fitted within each country and the results combined with a random-effects meta-analysis. The results were not adjusted for multiple statistical testing.

Additionally, posthoc analyses of change during the time between the initial and 1-year assessments were analysed using the same statistical methodology. However, in the hospital study data was not collected in the usual care group until the 1-year time point and therefore the effect of the 16-week physical activity and exercise intervention programme on steps per day and metres achieved in the ISWT was analysed using a paired t-test.

As the EPAF-Study was a "study within a study" the sample size was predetermined by the main EUROACTION trial (Wood et al., 2008) which used the EUROASPIRE II study (EUROASPIRE II Study Group, 2001) to estimate the coefficients of variation for sample means and proportions (Appendix 2). The EUROASPIRE study did not include steps or cardiorespiratory fitness data. Therefore, the power of the EPAF-Study could not be calculated "a priori" but was determined using expected mean differences that represent a clinically meaningful change at 80% power and 5% significance level.

Expected values for means steps per day were extrapolated from Tudor-Locke et al., (2009). They reviewed 60 unique studies and have usefully reported on mean steps per day in people with coronary heart disease, diabetes, hypertension and stroke. A later review by the same lead author (Tudor-Locke et al., 2011) of pedometer based interventions in healthy older adults and special populations identified a 10% increase in steps to represent a clinically meaningful difference. Based on this a sample size of 452 patients in both intervention and usual-care centres in each country was sufficient for detection of a 10% change in mean steps per day at the p=0.05 significance level with 80% power (Figure 3.9.1).

Figure 3.9.1: Sample size calculations

Measure	Mean (SD)	Number of patients needed in each intervention & usual care group (80% power and p=0.05)			
		% Change anticipated			
		5%	10%	15%	20%
Steps per day	6410 (3440)	1809	452	201	113
Metres scored ISWT	448 (138)	750	180	81	30
Minutes Chester Step Test	6.6 (2.48)	890	228	100	56

Sample size calculations were also derived for the ISWT based on expected values in coronary patients (Fowler et al., 2005) and the Chester Step Test (Cooney et al., 2013) (Figure 3.9.1). In both cases a 10% anticipated change was used as a minimum threshold as this exceeds expected differences due to learned effects (Buckley & Jones, 2011).

3.10: Assessment methodology

As illustrated in Figure 3.8.1 the physical activity assessment comprised of three measures; two in relation to physical activity participation (a seven day activity recall [7-DAR] and a recording of mean steps per day collected over seven consecutive days) and the last a measure of cardiorespiratory fitness (the ISWT in the hospital study and the CST in the general practice study). The methodology and results for the 7-DAR have been previously published as this measure was used for the main EUROACTION trial (Appendices 1 & 2), so will not be described further. The remaining measures have not been previously reported and the methodology applied is described below.

3.10.1 : Objective measurement of physical activity participation

Irrespective of assessment time point or research setting, the exact same methodology was applied to record seven consecutive days of pedometer readings by the Yamax Digiwalker SW-200. A standardised protocol was developed for collecting the pedometer data. Administering this protocol was covered in the training, reinforced in *The Health Professional Manual* and competency was ensured through quality assurance visits that followed.

The physiotherapists (and nurses where relevant) introduced the pedometer to each patient at a set point in the assessment. Standardised instructions were provided, which included a full demonstration and a supervised practice by each participant. These instructions were additionally supported in written form as part of the step counter logbook. All written instructions were provided in each of the languages and the translations were validated by an independent translation back into English, which was verified by the author. The importance of „acting as normal" was particularly emphasised given that wearing a pedometer may motivate walking behaviour temporarily. Likewise no information relating to national targets such as 10,000 steps per day was included. This was to avoid incentivizing activity during the measurement period.

Participants were instructed to wear the pedometer from the time they got up in the morning until last thing at night and to only remove the device for water-based activities such as showering, bathing and swimming. At the end of each day the exact number of steps was logged in their log book provided and the device reset to zero.

This same routine occurred for seven consecutive days, commencing the day following each assessment. Including seven consecutive days was important in appreciation that walking behaviour may differ considerably over a week‟s period (e.g. work versus leisure days, weekdays versus weekends etc). In instances where the participant did not collect data (e.g. forgot, lost device, failure of the device etc) this was also logged.

Patients attending the EUROACTION intervention returned their pedometers and step logbook at their first attendance to the programme. In all other instances participants were provided with a stamp addressed envelope and on completion of their logbook returned this, together with their pedometer. Consequently steps per day were entered into the database which was designed to automatically generate each participant‟s mean steps per day. A minimum of three days of data was required together with representation from both weekdays and weekends for this calculation to be valid.

In summary, the pedometer was worn the subsequent week to the assessment. Step data collected was analysed using two continuous variables (mean steps per day and proportion of patients achieving more than 10,000 steps per day on average) and one categorical outcome; (one of five activity classifications according to Tudor-Locke and Bassett, 2004) (Figure 2.4.2).

3.10.2: Measurement of Cardiorespiratory Fitness

Whilst maximal exercise tolerance testing is the gold-standard method to measure aerobic capacity this was not feasible given it carries a risk, requires specialist equipment, trained technicians and close monitoring of the cardiovascular responses e.g. electrocardiogram (Chapter 2). Consequently functional capacity was measured using submaximal exercise testing. There were no treadmills or bicycles available, nor the resources to supply these, resulting in a limited choice of options. Following a review of the literature the Incremental Shuttle Walk Test (ISWT) was selected for the coronary patients in the hospital study and the Chester Step Test for the asymptomatic patients at high multifactorial risk in the general practice study (Chapter 2).

Whilst it is appreciated that the same submaximal cardiorespiratory fitness test would have offered greater standardisation, this decision was based on two main reasons:

1. The two study populations were different. It was therefore appropriate to select the most valid and reliable tool for each population within the economic confines of the study. Review data identified the ISWT as a valid and reliable measure of peak oxygen uptake in coronary patients (Parreira et al., 2014). Despite this review including over 800 articles evaluating the ISWT, was no data of high enough quality in the general practice population. On the other hand, the CST has been evaluated in people at high cardiovascular risk and deemed useful for the assessment and management of CVD risk in a clinical setting (Stevens & Sykes, 1996; Buckley et al., 2004; Buckley & Jones, 2011; Cooney et al., 2013). There was no data on the validity or reliability of the CST in coronary patients.
2. The study settings were different. There was dedicated space in the hospital intervention centres as in this setting the physiotherapists were also delivering a group based supervised exercise programme. The usual care nurses each had access to a long enough hospital corridor that was conducive to carrying out the test. On the other hand, in general practice the physical activity assessments were carried out in small consulting rooms. The CST was a more feasible test to use in this setting given the limited space available.

3.10.2.1 : The Incremental Shuttle Walk Test

As justified by Chapter 2, the ISWT (Singh et al., 1992) was selected over a step test for use in the coronary patients across the 12 hospital centres. The test offers the greatest familiarity in walking on the flat; an accustomed activity for most. The ISWT was also selected above the six-minute walk test (6MWT) as it has been validated for use in coronary patients (Parreira et al., 2014), includes the advantage of an inbuilt warm up and also requires less space (Buckley & Jones, 2011).

The ISWT was developed by Singh and colleagues (1992) to measure disability in patients with COPD. It is an inexpensive tool that has also been used to assess exercise capacity in patients with cardiac disease (Houchen et al., 2012; Jolly et al., 2008; Tobin & Thow, 1999). The ISWT is a 12-level test (1 min in each level) imposing an incremental acceleration as the subject walks up and down a 10-metre course. In brief, two cones are set apart to provide a

between-cone distance of 9 metres. The walking speed is dictated by an audio signal. The speed starts at 0.50 metres per second (m/s) and is increased each minute by 0.17 m/s until a final speed (level 12) of 2.37 m/s (Figure 3.10.1). The test is finished when the subject is limited by dyspnoea or a heart rate (HR) > 85% predicted maximum or when the subject is unable to maintain the required speed and fails to complete a shuttle for a second consecutive time. The primary outcome is the distance covered in metres, calculated from the completed number of shuttles.

Figure 3.10.1: The Incremental Shuttle Walk Test Protocol

	Speed				Number of Shuttles	
Level	m/s	km/h	mph	Seconds/shuttle	In level	*Total
1	0.50	1.80	1.12	20.00	3	3
2	0.67	2.41	1.50	15.00	4	7
3	0.84	3.03	1.88	12.00	5	12
4	1.01	3.63	2.26	10.00	6	18
5	1.18	4.25	2.64	8.57	7	25
6	1.35	4.86	3.02	7.50	8	33
7	1.52	5.47	3.40	6.67	9	42
8	1.69	6.08	3.78	6.00	10	52
9	1.86	6.69	4.16	5.46	11	63
10	2.03	7.31	4.54	5.00	12	75
11	2.20	7.92	4.92	4.62	13	88
12	2.37	8.53	5.30	4.29	14	102

Each physiotherapist and usual care nurse was trained to administer the test during the central training and the testing protocol was reinforced by the *Health Professional Manual.* All were observed and assessed for competency in test administration during quality assurance visits which followed the training. Given there was a small risk of events during the test, the author assured that each tester held immediate life-support certification and in each centre there was an emergency procedure in place. This included access to a telephone to contact emergency services and a defibrillator within the facility itself.

In addition, to ensure safety, each participant was screened by the principle investigator (a medically trained doctor), prior to participating in the ISWT. The physiotherapists and nurses in usual care were additionally trained to carry out a standardised screening for the presence of any contraindications (Figure 3.10.2). Invitation letters and appointment related phone contact also ensured that patient‟s attended suitably dressed and prepared for the test. Those patients who did not fulfil the pre-test screening criteria were excluded from the test on that occasion and offered, where relevant, an additional appointment at a later date.

Figure 3.10.2: Pre-test Screening for the Incremental Shuttle Walk Test

Medical consent gained	□
Resting pulse regular and less than 100bpm	□
BP controlled (SBP<180) (DBP < 100)	□
No angina at rest or change in angina pattern	□
Subject taken all prescribed medication	□
Subject free from cold, sore throat or other temporary illness	□
Subject not on antibiotics	□
No hospital admissions (bar the recruiting event) in the past 4 weeks	□
No orthopaedic problems that could be exacerbated by exercise	□
If subject is diabetic, no hypoglycaemic episodes in past week	□
No signs of acute heart failure	□
No excessive alcohol consumed in the past 24 hours	□
No caffeine/ tobacco in the past 2 hours	□
No heavy meal in the past 2 hours	□
No strenuous activity 24 hours preceding the test	□
Subject is wearing suitable clothing / footwear	□
Subject gives informed consent	□

All equipment used for screening and test administration were standardised. Resting heart rate was determined using a Polar heart rate monitor, which was fitted to the patient on their arrival for the assessment. Blood pressure was measured using an automated sphygmomanometer. Once the patient was deemed suitable to participate in the ISWT the test end point for heart rate was determined using an age-adjusted formula, which also adjusted for chronotropic medications (e.g. betablockers), where indicated. An example is illustrated in Figure 3.10.3.

Figure 3.10.3: Calculating the end-point heart rate

Age-Adjusted Formula

Step 1: Estimation of heart rate maximum (HRmax)
220-age (-30 if betablockade therapy prescribed) = HRmax
Step 2: Submaximal end point determination of 85% HRmax
HRmax X 0.85 = test end point

The testing procedure was then explained using standardised instructions to the patient, including the purpose of the test, a description (i.e. set walking speeds where increases occur at one minute intervals, walking around the cones in time with the bleeps), monitoring of exercise intensity, warnings, the test end points and overall safety of the test. Consent to participate in the test was then reaffirmed. In addition prior to the test commencing the patient was familiarised to the Rating of Perceived Exertion (RPE) scale (Borg, 1998).

The ISWT was then carried out as per protocol (as summarised by Appendix 7), continuing in a progressive manner until the patient could no longer maintain the required speed, achieved the heart rate end point or became symptomatic. The metres achieved was then scored and recorded. Testers then entered the metres scored into the EUROACTION database.

3.10.2.2 : The Chester Step Test (CST)

In general practice both the population and the setting differed to the hospital study and for this part for the study the CST was employed. The CST was originally developed by Dr Kevin Sykes (1998) to assess aerobic fitness in fire fighters, the ambulance service, health authorities, and corporate institutions. As described in Chapter 2, the CST is one of many tests designed to provide a safe and practical means of assessing aerobic fitness under submaximal conditions. The limited equipment needed (step, heart rate monitor, compact disk player and RPE scale) and minimal space requirements made this an ideal test for the general practice settings.

Akin to the ISWT used in the hospital arm of the study the CST is a multistage incremental test involving „bleeps" but this time rather than setting a walking pace these provide a stepping pace. Every two minutes the rate increases and heart rate and RPE are collected. The test is designed to predict maximal oxygen uptake by extrapolation of these responses.

However, as the validity of this test to predict an actual maximum is questionable (Buckley et al., 2004) its use in this study was adapted. This standardised testing protocol, using a known step height, enabled a measurement of baseline fitness and expressed as the duration (in minutes and seconds) achieved on reaching either 85% HRmax or RPE 14/15 (Figure 3.10.4).

Figure 3.10.4: The Chester Step Test

Step Level	I		II		III		IV		V	
Steps / min	15		20		25		30		35	
Time	1	2	3	4	5	6	7	8	9	10
Heart rate recorded at each minute										
Exertion level (RPE scale) at each minute										
Score = time achieved in minutes and seconds										

As with the ISWT, the testing procedures were covered fully at the central training, reinforced by the *Health Professional Manual* and competency was assessed in quality assurance visits (Appendix 7). The principles of the CST were exactly the same in relation to pre-test screening, participant preparation and the need to calculate a heart rate end-point.

Whilst the explanation of the testing procedure was similar (e.g. purpose of the test, monitoring of exercise intensity, warnings, the test end points and overall safety of the test) the description of the test included a demonstration by the nurse and the opportunity for the patient to practice at stepping with both the right and the left leg leading in time with the metronome before the test started. As with the ISWT the patient was familiarised to the RPE scale and had to consent to participate in the test following receipt of these standardised instructions.

The CST was then carried out as per protocol (as summarised by Appendix 7), continuing in a progressive manner until the patient achieved the target heart rate or RPE end point, became symptomatic or in some instances could not coordinate with the set pace. The minutes and seconds achieved were then scored and recorded. Testers then entered the time achieved in minutes and seconds into the EUROACTION database.

3.11: The EUROACTION intervention

The EUROACTION study had two parts – a hospital and a general practice study. The two studies shared the same overall objectives to evaluate the effect of the EUROACTION intervention on physical activity participation (beyond subjective measures previously reported) and cardiorespiratory fitness. Whilst there are several features in the design of the physical activity and exercise intervention common to both studies there are also marked differences. The intervention in the hospital study lasted for 16-weeks and included a once weekly supervised group exercise programme, delivered by a physiotherapist working in conjunction with a multidisciplinary team. In general practice, the intervention lasted one year with monthly visits to a practice nurse who was trained to motivate changes in physical activity behaviour. There was no supervised exercise component in the general practice study. Given such clear distinctions, the following will describe the design of each study intervention separately.

3.11.1 : The EUROACTION intervention – hospital study

In the six hospital centres randomly allocated to deliver the intervention, the author worked closely with each of the physiotherapists in setting up the exercise programme. This included the ordering and supply of exercise equipment, the translation and production of standardised circuit cards for the supervised exercise programme together with home-based activity diaries and programme materials e.g. EUROACTION branded health promotion literature on the benefits of physical activity and exercise. The author ensured all translations were accurate with a re-translation back into English and for the programme materials additionally worked with the National Literacy Trust to ensure that readability was optimised.

The EUROACTION physical activity and exercise intervention in the hospital study comprised of four key elements: i. Exercise programme recruitment strategies; ii. The supervised exercise component; iii. The home-based activity intervention; and iv. The physical activity health promotion workshops.

i. Exercise programme recruitment strategies

Following the literature review the author (in association with the Steering Group and Central Management Team) employed three important strategies to enhance uptake to the exercise and activity programme. The first "*the active inclusion of partners"* has been featured in previous publications (Appendices 1 & 2) and will therefore not be discussed further. The second recruitment approach was the use of "*motivational invitation techniques".* The author, together with the nurse-coordinator, developed invitation letters that specifically included cognitive behavioural techniques as recommended in a review of randomised controlled trials by Davies et al., (2010). As part of the intervention, the physiotherapists also telephoned each participant to remind them of their assessment appointment time and how to come prepared to take part in a walking assessment. The training included the use of Motivational Interviewing (MI) delivered by the physiotherapists as part of this first telephone contact. The physiotherapists were trained to explore each patient‟s story in order to build rapport and collaboratively agree the agenda for the assessment session. The inclusion of this MI telephone contact was based on RCT data supporting its value in increasing uptake (Hillebrand, 1995).

The third and final recruitment approach employed was *"early programme orientation".* As part of the physical activity and exercise protocol all participants attended the initial assessment within ten days of being identified. During this assessment visit individuals (and their partners where relevant) received an induction session to the exercise programme with the physiotherapist. This design feature was included based on single-blind RCT evidence supporting the role of early programme orientation with improved attendance to cardiac rehabilitation (Pack et al., 2013b).

ii. The supervised exercise component

The EUROACTION physical activity intervention in hospital centres included a once weekly supervised group based exercise session, led by the physiotherapist. This weekly contact, over a 16-week period, allowed the physiotherapist to provide both a supervised aerobic endurance exercise session in a group setting and establish individualised exercise prescription for additional independent physical activity. The physiotherapists were trained to use a behavioural approach based on the S*tages of Change Model* described by Prochaska and DiClemente (Prochaska & DiClemente, 1998; Prochaska et al., 1992; Prochaska & DiClemente, 1984) and Motivational Interviewing techniques developed by Miller and

colleagues (Rubak et al., 2005; Rollnick et al., 1999; Miller & Rollnick, 1991). Given RCT evidence presented in Chapter 2, weekly goal setting was of paramount importance in this study protocol (Davies et al., 2010; Duncan & Pozehl, 2002; Sniehotta et al., 2006).

A summary of the overall structure of the supervised exercise component is provided in Figure 3.11.1. This intervention adopted the standards of the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR), a specialised clinical interest group based in the United Kingdom (ACPICR, 2009). This included adhering to health and safety regulations including emergency life-support training and provision, room temperature, humidity, staff to patient ratio and individual risk screening (including the collection of pre-exercise heart rate in all and blood pressure where indicated) prior to every session.

The exercise intervention was standardised across all six hospital centres. As illustrated, every country intentionally utilised an approach requiring minimal equipment in order to facilitate reproducibility in the home setting (Figure 3.11.2). This was essential as participants attended once per week and additional exercise training was required to achieve the doses required to provoke improvements in cardiorespiratory fitness.

Figure 3.11.1: The supervised exercise component

Exercise lead	▪ EUROACTION Physiotherapist
Facilitators	▪ EUROACTION nurse and dietitian
Staff to patient ratio	▪ 1:5
When?	▪ Following the initial assessment and exercise orientation session ▪ Daytime and evening times offered
Where?	▪ Hospital based
Frequency?	▪ Once weekly for 16 weeks
Format?	▪ 15 minute warm-up ▪ 20-30 minutes circuit-based conditioning component ▪ 10 minutes cool-down ▪ Followed by group based relaxation and/or health promotion workshops
Type	▪ Cardiovascular endurance exercise ▪ Minimal equipment ▪ Low skill

Figure 3.11.2: A minimal equipment approach to the exercise intervention

Halmstad, Sweden

Thiene, Italy

Valencia, Spain

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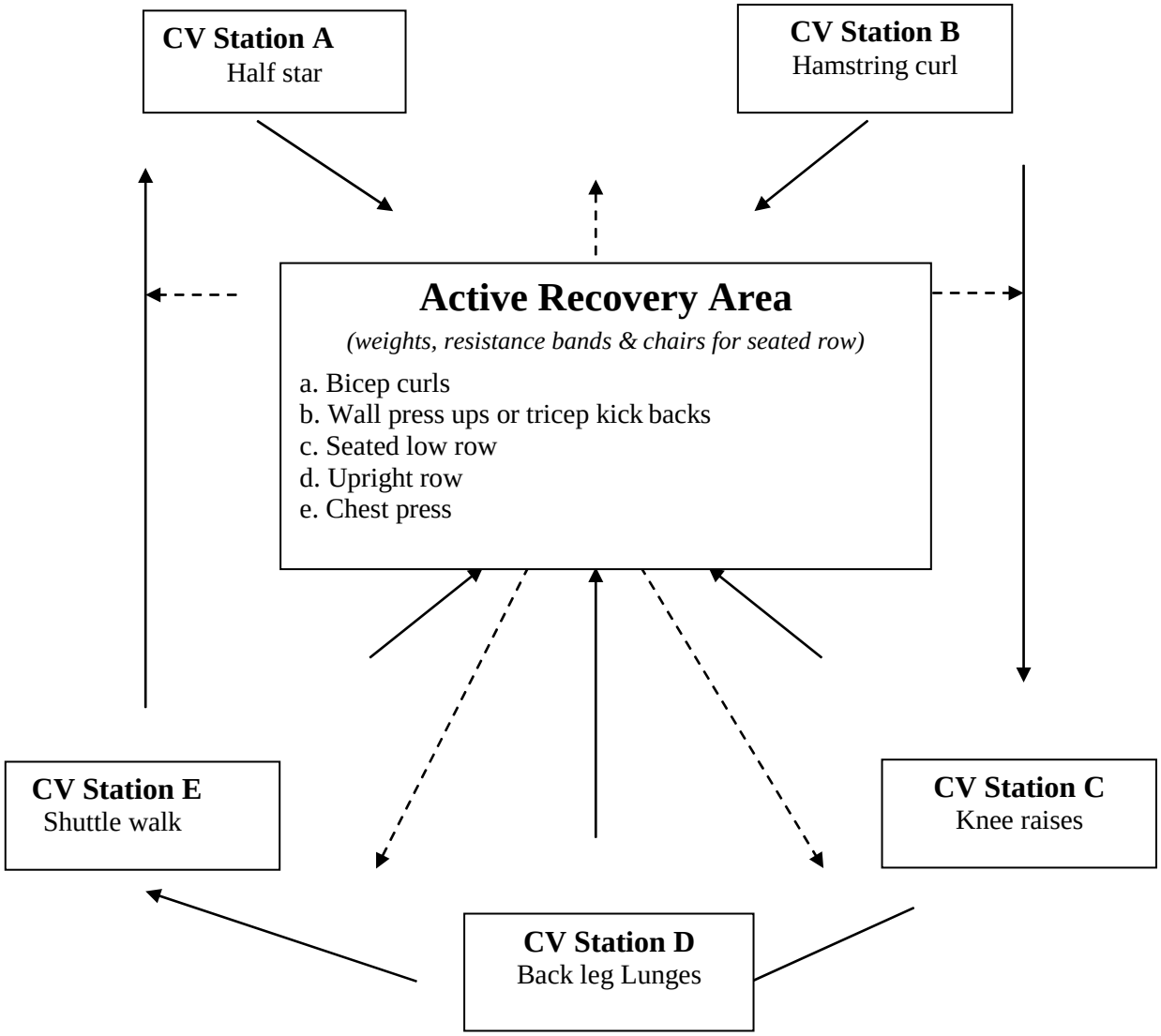
Every session began with a standardised group warm-up which formed an essential component providing the transition from resting state to a level of intensity which represented conditioning i.e. the intensity required to stimulate beneficial physiological adaptation. It lasted 15-minutes in total and was based on British recommendations (BACR, 2006). Whilst standardised the physiotherapist was trained to utilise the nurse and dietitian to offer alternatives and lower intensity options throughout (Appendix 8).

The main conditioning component was circuit-based and designed with the main objective of improving aerobic capacity and endurance. An interval-based approach was used progressing to continuous cardiovascular exercise. Interval training entailed bouts of relatively intense work interspersed with „active recovery" (AR). Active recovery involved interspersing predetermined periods of aerobic activity with muscular strength and endurance work (MSE). The exercise programme was purposefully designed to accommodate a group of individuals some of whom could only tolerate short intervals of aerobic activity whilst others were able to exercise continuously for 20-30 minutes within the recommended training heart rate ranges. This was achieved via a circuit design as shown in Figure 3.11.3 (BACR, 2006).

Figure 3.11.3: EUROACTION exercise circuit design (based on BACR recommendations, 2006)



This circuit based approach permitted some participants to adopt an interval approach whilst others could undertake continuous aerobic training. It offered a variety of exercise that could be adapted to accommodate individual needs and abilities as well as individuals to progress at their own rate, both within and between stations. Depending on the level of individual participants, they performed differing durations of continuous aerobic exercise before spending time in active recovery. For example a less able participant on level 1 completed 1 aerobic station followed by 1 MSE activity whereas a fitter client on level 4 completed 4 aerobic stations before performing a MSE activity. The aerobic stations were denoted by capital letters (ABCDE) and the MSE by small case (abcde). The aerobic station completed before determined the subsequent MSE exercise to be performed i.e. A to a, B to b etc.

The physiotherapist led the exercise session but the nurse and dietitian were also actively involved throughout. The conditioning component was followed by a 10-minute cool-down period aimed at preventing pooling of blood in the exercising extremities, avoiding symptoms such as dizziness, vertigo, syncope, palpitations, or nausea (Taylor et al., 2003). Maintaining gentle activity also reduced the risk of cardiac arrhythmias, which can, in high-risk individuals, result from high plasma catecholamine levels during the post-exercise period. The cool down essentially was the reverse of the warm-up with the exclusion of mobility exercises and the opportunity for developmental stretches. The aim of the cool-down was to lower heart rate to within ten beats of pre-exercise rates.

The issue of the intensity of exercise was critical for risk-benefit assessment. The cardiovascular system would not be stimulated sufficiently if the intensity was too low. However, a too vigorous exercise could trigger acute myocardial infarction (Taylor et al., 2003). Hence the intervention endorsed moderate intensity exercise, as this is associated with greater safety and greater adherence (Perri et al., 2002). Consequently the physiotherapist calculated a training heart rate range, representing 40-60% VO_2max for each individual using the long-established Karvonen formula (Karvonen et al., 1957). This was further adjusted for chronotropic medications (i.e. betablockers) where relevant. In recognition that using heart rate in isolation as a measure of exercise intensity has a number of limitations Rating of Perceived Exertion (RPE) (Borg, 1998) and direct observation were also employed.

In summary, the supervised exercise component used in the hospital intervention centres was a once-weekly group-based exercise session led by the physiotherapist and aimed specifically to develop each individual‟s cardiorespiratory fitness through a progressive cardiovascular endurance-based programme. The initial exercise prescription was based on the baseline assessment findings, including risk stratification, and monitored closely. Weekly reviews allowed for progression both for the supervised and home exercise prescriptions. Partners and family were also encouraged to attend, aiming to develop important social support mechanisms to sustain increases in physical activity in the long term. Given that a frequency of two to three times a week of structured activity is required to ensure the achievement of gains in exercise capacity the weekly supervised exercise was supplemented with a tailored home-based activity programme.

iii. The home-based activity intervention

As identified in Chapter 2 it is cardio-respiratory endurance training which confers the physiological changes known to reduce symptoms and mortality in cardiac patients. Consequently, achieving effective doses of aerobic exercise was the main focus of the activity intervention overall. This was achieved by a combination of supervised exercise together with structured activity in the home setting. Strong emphasis was also given to encouraging general physical activity as part of every-day living in recognition that expending more kilocalories over the course of a day is associated with a number of health-related benefits.

Hence the physiotherapists had the challenge of encouraging physical activity on a daily basis as well as providing an effective thrice weekly exercise prescription purposefully aimed at increasing cardiorespiratory fitness. Each therefore designed individual home-based exercise plans to include two further sessions to complement the once weekly supervised session. This was extremely important given that the ultimate goal was to equip individuals to become responsible for their physical activity long-term. The home exercise prescription included a once weekly structured walking programme and a once weekly home-based circuit.

For the walking-based programme participants were encouraged to wear a pedometer and achieve the goals in steps per day that are set at the weekly reviews with the physiotherapist. The use of the pedometer in these instances acted as a motivational tool and the opportunity for participants to record activity more objectively. They kept a record of their steps achieved in their home activity diary. For the home-based circuit, participants essentially repeated the supervised component in their home setting and recorded their rating of perceived exertion in their activity diaries. Weights were replaced by household products such as a bag of rice and all participants were supplied with a length of resistance band.

In addition to structured activity above the physiotherapists encouraged participants to become more physically active on a daily basis (Figure 3.11.4). Home exercise and activity were recorded in a physical activity diary, which was then reviewed and progressed accordingly at the weekly supervised sessions by the physiotherapist.

Figure 3.11.4: Examples used to encourage increased activity as part of every-day life

- On non-exercise training days participate in at least 30 minutes of physical activity per day.
- Minimise sitting time. For every hour sitting make sure you get up and move for at least 2 minutes.
- Walk to work.
- Using the stairs instead of the lift.
- Getting off the bus one stop earlier and walking the rest of the journey.
- Cycle wherever it is safe to do so.
- Gardening - when gardening, take a brisk walk around the garden every 10 minutes or so before returning to the task.
- Park the car in the furthest car parking space or the next street and walk to the destination.
- While talking on the phone do some knee bends or walk around.

The physiotherapists gathered as much information about physical activity opportunities and exercise session availability, activity choice, location, accessibility and cost in their local areas. A „menu" of activities was consequently compiled and available to participants as a resource to facilitate continued activity following programme completion at 16-weeks.

iv. The physical activity health promotion workshops

The fourth and final component of the physical activity intervention was the delivery of two interactive workshops. Within every 16 week period, each physiotherapist facilitated a forum for discussion; one session focussed on physical activity and health and another concerning fitness and health. These two workshops provided educational information on the benefits of physical activity and exercise and facilitated a better understanding of managing cardiovascular disease and preventing further disease through the right type and amount of activity.

3.11.2: The EUROACTION intervention – general practice study

The EUROACTION physical activity intervention in the general practice study used exactly the same recruitment techniques as described in Section 3.11.1. However the design of the physical activity intervention itself was quite different. This entailed a practice nurse who was trained to use Motivational Interviewing (MI) to elicit a change in physical activity behaviour over a 12 month period. The practice nurses delivering the intervention typically reviewed patients on a monthly basis; addressing not only physical activity but also diet, psychosocial well-being and the management of medical risk factors.

The physical activity intervention comprised of a pedometer-based programme. Participants kept a diary of their step counts which was reviewed monthly with the practice nurse. The nurses were trained to use MI approaches and goal setting. MI is a directive client centred counselling style that was incorporated to assist the patients in exploring and resolving ambivalence to increase motivation for change (Rubak et al., 2005). Once change action had occurred the nurses were encouraged to incorporate cognitive behavioural techniques to maintain change in the same way as a very well documented summary by Narr-King et al., (2013).

The nurses were trained to specifically explore each participant‟s activity preferences and their barriers. Each individual entered into the programme with a different combination of feelings, support, motivation, belief structure, perception and set of goals and as such the nurses were required to tailor their advice and set activity goals that were sensitive to these important factors. For those that expressed interest in structured activities the protocol was for the nurses to sign post to localised opportunities.

The physical activity intervention in the general practices was centred on “Stage of Change” (Prochaska & DiClemente, 1998; Prochaska et al., 1992; Prochaska & DiClemente, 1984). The practice nurses in general practice were trained to formally assess and identify the patient‟s stage of change and then administer the most appropriate exercise intervention (Figure 3.11.5). For example, with a patient who was found to be „contemplating‟ whether to take up structured activity the practice nurse was trained to provide information, written and verbal, assisting the individual in their decision making process, formed from weighing up their perceived pros and cons. Pro or positive features for exercising included, for example enhanced confidence, feeling good about oneself and having more energy for one‟s family

and friends. Con or negative factors conversely included for example, being too tired to exercise, feeling uncomfortable and out of breath, and not having enough time. Knowledge of individuals‟ pros and cons was essential to designing an effective activity programme. Health promotion interventions, therefore, needed to focus on increasing participants‟ pros of exercise in order for movement to occur through the stages. Most of the EUROACTION participants were in the action stage and many were new to increased activity behaviour and hence needed support, positive reinforcement and the employment of specific techniques, such as motivational interviewing to increase self-efficacy.

Once effective exercise behaviour had been maintained for longer than six months, the individuals reached the maintenance stage of this model and needed assistance to identify triggers that could result in relapse as well as possible strategies to overcome these. The practice nurses were trained to prepare individuals for relapse, highlighting this as a learning experience rather than a failure to succeed.

The process for changing patterns in physical activity specifically was to use „bite-size‟ goals, where the practice nurses provided continued support and encouragement at every consultation. This way activity levels would gradually increase with simultaneous gains in self-efficacy. The overall aim of the intervention was to achieve the European recommendations for physical activity through individualised goal setting, regular monitoring and review, and the involvement of partners and family members; essentially with the overall ambition to empower families to sustain a more active lifestyle.

3.12 Quality assurance

Quality assurance visits across all 8 countries took place at set intervals. The first visit occurred 1 month after the central training. The author visited each of the physiotherapists and nurses and observed them administering the physical activity and exercise assessment. In the intervention centres this visit extended to include observing the programme in action. Three further quality assurance visits took place subsequently; at 3 months, 6 months and 9-months following the training. These visits however were carried out by the Senior Research Fellow. The author carried out a second quality assurance visit when the 1-year follow-up period begun and observed the final assessment being administered by each of the physiotherapists and nurses.

Figure 3.11.5: Physical activity intervention and 'Stage of Change'

From precontemplation toward contemplation

- no serious intention to change
- really do not want to change to become physically active

✓ Provide accurate information and convincing or compelling evidence. Help them to see and appreciate the benefits of becoming more physically active

✓ Emphasise the short-term benefits of being active, e.g. feeling invigorated, sleeping better etc

✓ Explore possible mechanisms about being regularly active and assist people in identifying ways to overcome them.

From contemplation towards preparation

- thinking about becoming physically active, but not yet committed
- barriers outweigh what they perceive to be the benefits of an active lifestyle

✓ Help them to specifically identify their barriers to change, determine what is standing in their way

✓ Help them weigh up the pros and cons of being physically active

✓ Help them to set small specific goals such as „I will walk the dog for 10 minutes each day", rather than „I will be more active each day."

From preparation toward action

- may be ready to begin, or may currently exercise but not regularly
- may have a plan but not know what they need to do

✓ Help develop a plan for regular activity and emphasise small, specific and realistic goals

✓ Reinforce attempts to become more active

From action toward maintenance

- have been active for less than 6 months
- particularly at risk of reverting to old patterns

✓ Provide positive, direct and appropriate feedback to build self-confidence and self-efficacy

✓ Explore and develop a menu of activities that will reduce risk of injury and boredom.

✓ Identify episodes when they had brief lapses and explore underlying reasons.

To encourage continuation – in „Maintenance"

- successfully sustained the physical activity for more than 6 months
- periods of lapses may have occurred

✓ Help them recognise and appreciate their self-confidence

✓ Encourage them to build variety into the physically active lifestyle. Keep it fun!

3.13 Summary

The main EUROACTION study previously published positive outcomes for physical activity participation in a comparison between intervention and usual care at 1-year. However, this was based entirely on self-reported (i.e. subjective) measurement. This study, the EPAF-Study, comprised of 2 parts and set out with a common agenda; to more rigorously evaluate the EUROACTION programme in relation to physical activity participation and cardiorespiratory fitness in: i. coronary patients and ii. apparently healthy individuals found to be at high multifactorial risk for developing CVD. The outcome measures for objective physical activity participation were mean steps per day and proportion of patients achieving greater than 10,000 steps.

The assessment for cardiorespiratory fitness differed between the two settings. In the hospital component the outcome measure used was distance achieved in the Incremental Shuttle Walk Test, whilst in the general practice part time achieved in the Chester Step Test was used. There were also some differences in the assessment time points between the hospital study and that in general practice. The latter was able to include objective assessment of physical activity participation and fitness at the initial assessment, allowing for additional analysis of the difference „*in the difference"* in change over 1-year between the intervention and usual care centres.

The physical activity and exercise intervention also differed between the hospital and general practice settings. The latter used practice nurses in both the intervention and usual care centres. Here, intervention nurses delivered a 1-year intervention that was based around motivational interviewing, cognitive behavioural techniques and goal setting. The hospital intervention was entirely different; physiotherapists delivered a once weekly supervised exercise programme coupled with a home-based activity plan over the course of 16-weeks.

Given such distinctions in the study methodology, it is more logical to present the results separately for the hospital and general practice studies. Chapters 4 and 5 that follow present a summary of the findings for each part of this study respectively. In setting the scene for later discussions, Chapters 6 will supplement previously published data to describe the baseline characteristics of the population, study recruitment and any loss to follow-up.

Chapter 4: Results 1

Identification, eligibility and recruitment of patients in hospital and general practice

4.1: *Identification, eligibility and recruitment of patients in hospital and general practice*

4.2: *Characteristics of coronary and high risk patients in hospital and general practice*

4.3: *Characteristics of those who participated in the EUROACTION cardiovascular prevention and rehabilitation programme*

4.4: *Summary of the "EPAF-Study" population and recruitment and attrition*

This Chapter aims to describe the study population for the coronary patients in the hospital study and the high risk individuals in the general practice study. This is important in the context of preparing for the subsequent discussions. Knowledge of any differences in recruitment or participant characteristics together with awareness of what proportion of people dropped out are all essential ingredients to interpreting this study's findings and identifying its limitations. This Chapter will present the identification, eligibility and study recruitment as published previously in the Lancet (Wood et al., 2008) (Appendix 2). This Chapter offers an extension to these previously published findings from the EUROACTION trial by including a number of additional new and post-hoc analyses.

4.1: *Identification, eligibility and recruitment of patients in hospital and general practice*

Over a two-year period the EUROACTION study identified 5,797 patients from 24 centres (12 pairs), across 8 European countries. The following will present the identification, eligibility, recruitment and participation, for both the intervention (INT) and usual care (UC) hospital and general practice parts of the study.

4.1.1: Recruitment in the hospital part of the study

Six pairs of comparable hospital centres were randomised for treatment allocation. A similar numbers of patients were subsequently identified in each arm of the hospital study (1,694 INT versus 1,718 UC) resulting in a total of 3412 patients overall (Table 4.1.1). This highlights that the overall population size identified in INT versus UC hospitals was highly comparable.

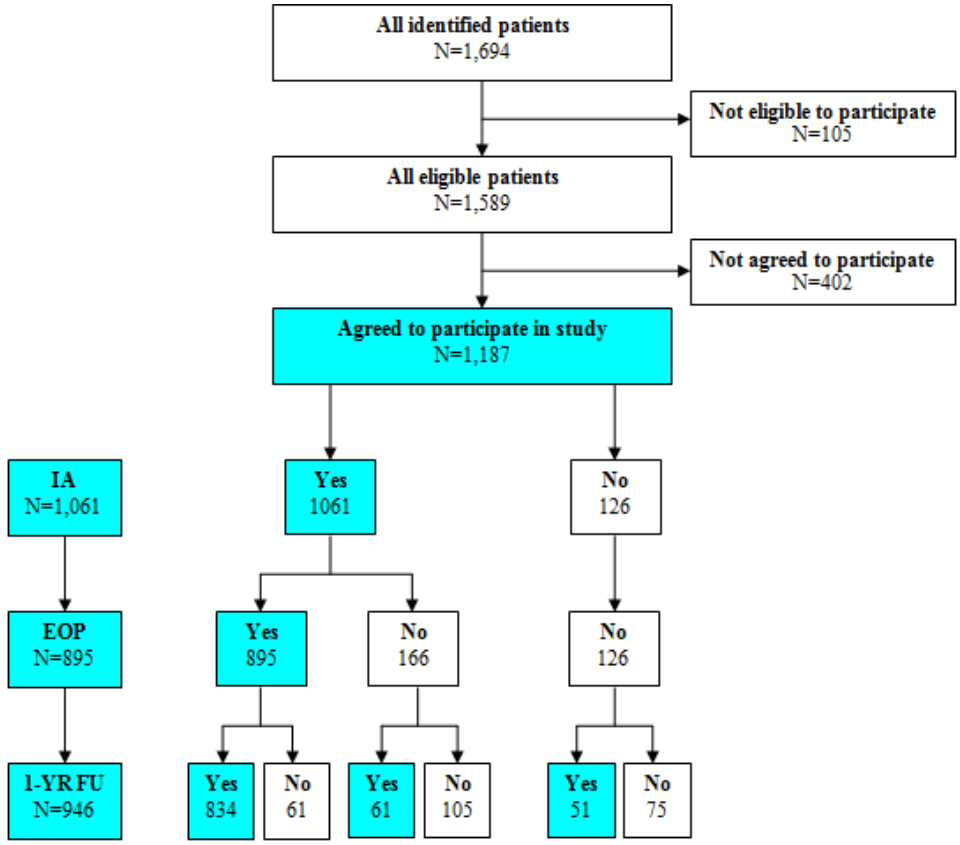
Table 4.1.1: Summary of design and recruitment for the *Hospital* study (⁘)

	Intervention	**Usual Care**
	Patients	**Patients**
Identification	1694	1718
Eligible	1589 *(∞94%)*	1499 *(∞87%)*
Consented to the EUROACTION intervention programme	1187 *(*75%)*	NA
Initial assessment	1061 *(*67% +89%)*	307~
Full participation in the programme	860 *(*54% +75% **82%)*	NA
One-year assessment	946 *(* 60% +80% **89%)*	994 *(* 66%)*

∞ of all those identified; *of those eligible; + of those who consented, **of those who attended initial assessment; ~ Random sub-sample

(⁘) As published in the Lancet (Appendix 2)

All patients were identified through medical records by the nurse in each centre. Of the 1694 patients identified by the intervention centre 94% were found to be eligible. Of these 25% did not agree to participate (Figures 4.1.1). The vast majority of those who were eligible gave their informed consent and then participated fully, attending the initial assessment (89%), the end of programme assessment (75%) and the 1-year follow-up (80%). All patients who had agreed to participate were invited to the 1-year follow-up, irrespective of previous attendance. 51 patients who had not attended the IA or programme did return at 1 year together with a further 61 who had attended the IA but not completed the programme. As such intention to treat analyses were carried out.



IA = Initial assessment EOP = End of programme assessment 1-YR FU = 1-year follow-up assessment

Figure 4.1.1: Summary of flow of patients for the *Hospital Intervention* (⁂)

(⁂) As published in the Lancet (Appendix 2)

In UC patients were identified in the same way as for the INT arm, but only contacted at 1-year where they were then screened for eligibility. However, in order to assess for comparability at baseline a random subsample of usual care patients (n=307) were invited to attend an initial assessment (20% of all eligible patients) (Table 4.1.1).

4.1.2: Recruitment in the general practice part of the study

Six pairs of comparable general practice centres were randomised for treatment allocation. A similar number of patients were identified in the INT (n=1,257) and UC (n=1,128) arms. This highlights that the overall population size identified for INT versus UC was also highly comparable for the general practice part of the study.

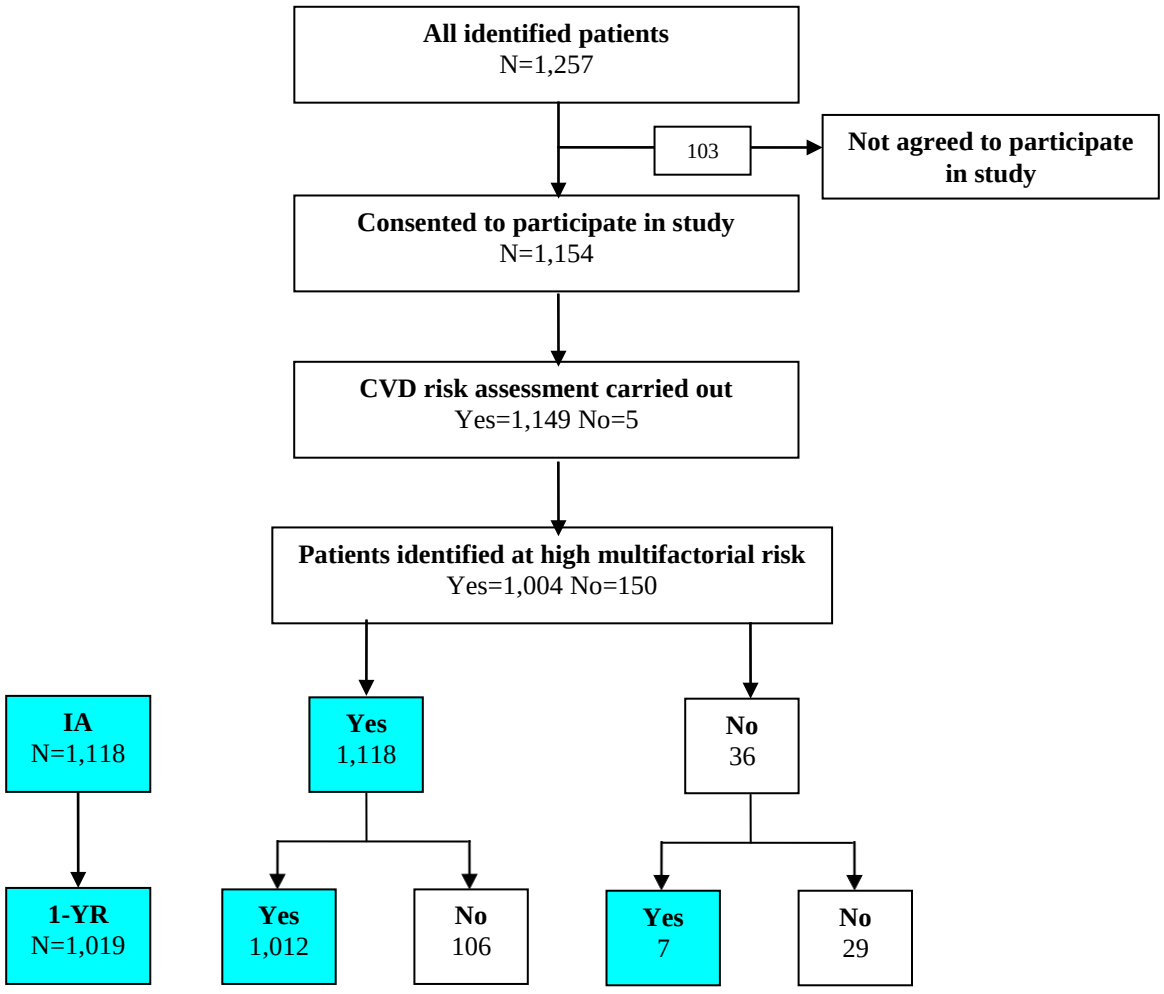
Of the 1,189 eligible patients identified by the general practice intervention centres 95% agreed to participate and almost all (>99.5%) underwent a cardiovascular risk assessment. Of these 97% then attended the full initial assessment (Table 4.1.2). This uptake for the general practice study was significantly higher than that observed in the hospital arm (95% versus 75% respectively) which is surprising given that these are otherwise apparently healthy individuals. In addition there was very little drop-out with 91% of patients who had attended the initial assessment returning for their 1-year assessment (Figure 4.1.2). At 1-year (the primary end point for the main study) the absolute number of patients was approximately equal for INT versus UC; 1,019 versus 1,005 respectively.

Table 4.1.2: Summary of design and recruitment for the *General Practice* study (⁘)

	Intervention	**Usual Care**
	Patients	**Patients**
Identification	1257	1128
Eligible	1189 *(∞95%)*	NA
Consented to the EUROACTION intervention programme	1154 *(*97%)*	NA
Initial assessment	1118 *(*94% +97%)*	~332
Full participation in the programme	947 *(*80% +82% **85%)*	NA
One-year assessment	1019 *(*86% +88% **91%)*	1005 *(∞89%)*

∞ of all those identified; *of those eligible; + of those who consented, **of those who attended initial assessment; ~ Random sub-sample

(⁘) As published in the Lancet (Appendix 2)



IA = Initial assessment 1-YR = 1-year assessment

Figure 4.1.2: Summary of flow of patients for the *General Practice Intervention* (⁘)

(⁘) As published in the Lancet (Appendix 2)

As with the hospital study all UC patients were identified at the outset but only a random subsample were contacted at the outset and invited to attend an initial assessment (20% of all those identified). The remaining UC patients were invited for the first time at 1-year together with a rescreening of the UC subsample (Table 4.1.2).

4.1.1: Summary

In summary, an excellent balance was achieved overall with regards to absolute numbers for the primary analyses comparing physical activity participation and cardiorespiratory fitness in INT with UC at 1-year. A greater proportion of INT patients agreed to participate in the general practice arm of the study than that seen in hospitals (95% versus 75% respectively) but in both cases once patients had attended the initial assessment there was very little drop out.

4.2: Characteristics of coronary and high risk patients in hospital and general practice

The EPAF-Study was a study nested within the main EUROACTION trial. The following will present the characteristics of this predetermined study population together with recruitment by centre, age and sex in both patient groups and recruiting diagnosis. These are pertinent analyses to explaining possible differences seen later in the results for this EPAF-Study evaluating physical activity participation and cardiorespiratory fitness.

Whilst acknowledging the primary focus of this study relates to activity and exercise the baseline characteristics included within highlight all aspects of lifestyle (smoking, diet and activity) as well as the management of medical risk factors (blood pressure, lipids and glucose). This is provided to give an appreciation of the significant challenges faced by both the hospital and general practice teams, where the vast majority of individuals recruited were not meeting the European recommendations for CVD prevention across many risk factors. This is an important acknowledgement as whilst this study concerns physical activity and exercise, its intervention was delivered as part of a multifactorial programme in patients having to address many other concurrent risk factors.

4.2.1: Recruitment by centre, age, sex and recruiting diagnosis

Recruitment across the 8 European countries differed widely resulting in a highly heterogeneous study population overall ($p<0.0001$) (Table 4.2.1 & Table 4.2.2). For example, in the hospital arm of the study the intervention centre in Italy recruited the most patients (22.8%) whilst its usual care centre had one of the lowest rates of recruitment (15%). The intervention centre in France on the other hand had the lowest rate of recruitment for the entire study (9%) and yet its usual care centre's recruitment was well above average (17.4%). The same can be said for general practice where country and within country variations were apparent.

According to the Mann-Whitney test, there was no significant difference in the mean age (63 years) of 946 INT and 994 UC hospital patients (Table 4.2.1). In general practice however, the mean age of 1,019 INT (62 years) and 1,005 UC patients (62.8 years) was significantly different ($p=0.004$) (Table 4.2.2). The INT arm had a greater proportion of younger patients (<55years) than UC; 22.2% versus 14.8% respectively ($p<0.0001$).

When analysing age range for each part of the study, hospital INT versus UC and general practice INT versus UC, the proportions within each group (< 55, 55-64 and > 65 years) were similar. Unsurprisingly, a greater proportion of patients were over 65 in the hospital arm (coronary patients with disease) compared to the general practice arm (asymptomatic apparently healthy individuals at high risk of developing disease).

With regards to sex, using the same statistical testing, in the hospital arm of the study whilst 70% of coronary patients were male this was comparable in both INT and UC (p=0.99) (Figure 6.2.1). In general practice whilst there was a more equal split between the sexes (50% of INT and 57% of UC patients being male) there were more males in UC than in INT (p<0.0006) (Table 4.2.2).

Finally, whilst for the hospital arm of the study mean age and sex were highly comparable between the 946 INT and 994 UC coronary patients there were significant differences in their recruiting diagnoses. The hospital INT arm recruited a greater proportion of patients with stable angina than UC (36% versus 25% respectively), whereas the latter recruited more patients' post myocardial infarction or with unstable angina (p<0.0001) (Table 4.2.1).

In general practice there were again significant differences in recruiting diagnoses, predominantly in that UC recruited more individuals into the HeartScore group (51% UC versus 42% INT) whereas INT recruited more patients already on treatment for blood pressure or cholesterol and patients with known diabetes (p=0.0006) (Table 4.2.2).

Table 4.2.1: Coronary patient characteristics: distribution of age, sex, recruiting diagnosis and country

	INTERVENTION N=946	**USUAL CARE** N=994	Significance
Country			P<0.0001*
France	9.0% (85/946)	17.4% (173/994)	
Italy	22.8% (216/946)	15.0% (149/994)	
Poland	20.8% (197/946)	19.1% (190/994)	
Spain	15.0% (142/946)	18.9% (188/994)	
Sweden	14.4% (136/946)	15.6% (155/994)	
UK	18.0% (170/946)	14.0% (139/994)	
Sex			P=0.99*
Men	69.9% (661/946)	69.9% (695/994)	
Women	30.1% (285/946)	30.1% (299/994)	
Age			P=0.59 $^{\alpha}$
< 55 years, %	22.2% (210/946)	21.9% (218/994)	
55-64 years, %	35.3% (334/946)	33.4% (332/994)	
≥ 65 years, %	42.5% (402/946)	44.7% (444/994)	
Mean (SD)	62.5 (9.90)	63.0 (9.64)	P=0.43 $^{\alpha}$
Recruiting diagnosis			P<0.0001*
Acute myocardial Infarction	47.7% (451/946)	53.6% (533/994)	
Unstable angina	16.5% (156/946)	21.1% (210/994)	
Stable angina pectoris	35.8% (339/946)	25.2% (251/994)	

* According to Chi-square test or $^{\alpha}$ the Mann-Whitney test;

Table 4.2.2: High risk patient characteristics: distribution of age, sex, recruiting diagnosis and country

	INTERVENTION N=1019	**USUAL CARE N=1005**	Significance
Age**, % (n)			P<0.0001 [α]
< 55 yr	**22.2% (226/1019)**	**14.8% (149/1005)**	
55-64 yr	43.9% (447/1019)	48.4% (486/1005)	
≥ 65 yr	34.0% (346/1019)	36.8% (370/1005)	
Mean (SD)	62.0 (7.6)	62.8 (7.3)	P=0.004 [α]
Sex, % (n)			
Female	50.2% (512/1019)	42.6% (428/1005)	P=0.0006*
Male	49.8 (507/1019)	57.4 (577/1005)	
Recruiting diagnosis			
Smoking	30.8% (312/1013)	31.5% (298/946)	P=0.77*
Elevated BP	34.8% (352/1013)	35.8% (352/984)	P=0.64*
AH drug therapy	**40.4% (411/1018)**	**25.9% (260/1005)**	P<0.0001*
Elevated cholesterol	**69.1% (694/1004)**	**62.7% (613/978)**	P=0.003*
LL drug therapy	**16.0% (163/1017)**	**12.6% (126/1003)**	P=0.03*
New diabetes	**16.0% (162/1013)**	**9.0% (90/1003)**	P<0.0001*
Known diabetes	15.4% (156/1015)	17.6% (176/1004)	P=0.21*
Risk groups			P=0.0006*
Group A	**42.3% (431/1019)**	**50.8% (511/1005)**	
Group B	26.7% (272/1019)	22.9% (230/1005)	
Group C	31.0% (316/1019)	26.3% (264/1005)	
Country			P<0.0001*
Denmark	10.2% (104/1019)	15.3% (154/1005)	
Italy	16.2% (165/1019)	19.3% (194/1005)	
Netherlands	18.7% (191/1019)	12.2% (123/1005)	
Poland	23.0% (234/1019)	15.9% (160/1005)	
Spain	19.5% (199/1019)	19.2% (193/1005)	
UK	12.4% (126/1019)	18.0% (181/1005)	

* According to Chi-square test or [α] the Mann-Whitney test; ** age at final assessment

AH = antihypertensive LL = lipid lowering

Group 1 = HeartScore ≥ 5%
Group 2 = On treatment for BP-lipids
Group 3 = Known diabetes

4.2.2: Lifestyle characteristics (smoking, diet and physical activity) of coronary patients and high risk patients at the initial assessment

In the 12 EUROACTION intervention centres across the study (6 in hospital and 6 in general practice) all eligible patients who had consented were invited for an initial assessment which involved a detailed review of their smoking habits, diet and physical activity status together with measurement of psychosocial health and the management of their medical risk factors. A random subsample of UC patients underwent the same initial assessment to ascertain baseline comparability between INT and UC. It is important to ascertain if the health profiles of INT and UC were the same overall to draw more robust conclusions as to the impact of the programme.

4.2.2.1: Smoking, diet and physical activity in coronary patients

Of the 1061 INT coronary patients who attended the initial assessment, the prevalence of smoking at baseline was low and comparable for INT and UC patients (12% versus 15% respectively) (Table 4.2.3). In contrast the dietary profile, whilst comparable between INT and UC, was appalling; Saturated fat intake was high and fruit and vegetables, fish and oily fish consumption was low (Table 4.2.3). Physical activity was assessed in part by an interview administered 7-day physical activity recall questionnaire. At baseline 74% of INT patients and 76% of UC patients were not achieving the European goal for physical activity (Table 4.2.3).

In accordance with the poor dietary and physical activity profile, 78% and 77% of INT and UC coronary patients respectively were overweight (body mass index $\geq$25 kg.m^{-2}) at the initial assessment (Table 4.2.3). Central adiposity was present with 74% of INT patients and 72% of UC patients having an unhealthy waist circumference ($\geq$ 94 cm men; $\geq$80 cm women).

4.2.2.2: Smoking, diet and physical activity in high risk patients

Of the 1118 INT and 332 UC subsample patients at high risk of CVD who attended the initial assessment 31% were current smokers. The diet of high risk patients was again far from optimal (Table 4.2.3) and comparably poor in both INT and UC. The interview administered 7-day activity recall revealed that 29% of all INT patients and 32% of UC patients were achieving the physical activity target. Low levels of activity were confirmed by a mean number per steps of 6690 ($\pm$ 3415) step counts in INT and 6193 ($\pm$ 3520) step counts in UC. Cardiorespiratory fitness was also similarly low at the initial assessment in both INT and UC (Table 4.2.3).

In accordance with the poor dietary and physical activity habits of these patients over 80% of all patients at high CVD risk at the initial assessment were overweight (body mass index >25kg.m^2). Central adiposity was highly prevalent where more than 80% of all patients presented with a waist circumference $\geq$ 94 cm in men and $\geq$80 cm in women (Table 4.2.3).

4.2.3: Summary

When analysing recruitment by centre, age, sex and recruiting diagnosis significant differences were found. There was great heterogeneity found between countries and within countries for both the hospital and general practice arms of the study. Whilst there were no significant differences in age or sex between hospital INT and UC overall, significantly more patients were recruited following an acute myocardial infarction and with unstable angina by the UC arm as opposed to the INT arm who recruited more patients with stable angina. In addition, the coronary patients tended to be male and were generally older than the population in the general practice study.

In general practice although there was a more equal split in that 54% of patients overall were male there were significantly less males in the INT group compared to UC. In addition the INT group were significantly younger with more individuals under the age of 55 years. The INT group recruited more people either on treatment already for raised blood pressure or cholesterol or with known diabetes whereas in UC significantly more patients were recruited through new identification of risk (HeartScore >5%).

Despite significant differences in age, sex and recruiting diagnosis the health profile of patients in INT and UC were similar. The baseline lifestyle characteristics reveal a similarly low prevalence of smoking in INT and UC. The vast majority of patients and partners were not following a cardioprotective diet and few engaged in physical activity at baseline. Most individuals at baseline were overweight and centrally obese with poorly controlled blood pressure and lipid profiles. Of particular relevance for this study there were no significant differences at baseline in physical activity participation between INT and UC.

Table 4.2.3: Health characteristics of coronary and high risk patients

	Hospital		General Practice	
	Coronary patients		High risk patients	
	INT n=1061	UC n=306	INT n=1118	UC n=332
Not smoking (confirmed by CO test)	88.2% (933/1058)	84.8% (256/302)	68.6% (761/1110)	68.6% (225/328)
Saturated Fat <10% of total energy*	43.2% (64/148)	35.5% (38/107)	NA	NA
Oily fish ≥3x/week	3.1% (33/1060)	4.9% (15/304)	5.0% (55/1094)	3.0% (10/331)
Fish ≥20 g/day	55.6% (589/1060)	58.6% (178/304)	62.0% (680/1096)	65.6% (217/331)
Fruit and vegetables ≥400g/day	45.3% (480/1060)	28.0% (85/304)	50.1% (548/1093)	35.4% (117/331)
Physical activity ≥30minutes, ≥4x/week	**25.9%** (273/1056)	**24.3%** (74/304)	**29.0%** (313/1080)	**32.3%** (107/331)
Mean steps per day (SD)	**NA**	**NA**	**6690.9 steps** (3415.6)	**6193.2 steps** (3519.6)
Minutes achieved CST (SD)	**NA**	**NA**	**6.60 minutes** (2.48)	**6.81 minutes** (2.36)
BMI<25kg/m^2	21.7% (229/1057)	23.4% (71/303)	19.1% (209/1094)	18.4% (61/331)
Ideal waist circumference (men <94cm; women<80cm)	25.8% (272/1056)	28.1% (84/299)	19.5% (212/1087)	16.9% (56/331)

**Random sub-sample only; NA: not available; CST: Chester Step Test*

4.3: *Characteristics of those who participated in the EUROACTION cardiovascular prevention and rehabilitation programme*

Across 12 intervention centres, 6 in hospital (coronary patients) and 6 in general practice (high risk patients) a total of 2,341 eligible patients consented to take part in the study. However of these 22% (n=524) did not then participate fully in the EUROACTION cardiovascular prevention and rehabilitation programme. The following will present the characteristics (age, sex, diagnosis and country) of the 870 coronary patients who did participate in the intervention programme compared to the 317 individuals who did not participate at all. Likewise the same comparison is presented for the general practice study, 947 versus 207 high risk patients respectively. These are important analyses in quantifying possible selectivity of patients in the intervention arm.

6.3.1: EUROACTION coronary patients

Of the 1,589 eligible coronary patients in the intervention arm 75% consented to participate (n=1187) but of these 1061 attended the initial assessment. Using medical records age, sex and recruiting diagnosis were compared (Table 4.3.1). Patients who did not consent or who did consent but then did not attend the initial assessment were older ($p<0.0001$), more likely to be female ($p=0.04$) and more likely to be those with a recruiting diagnosis of unstable angina ($p<0.0001$) (Table 4.3.1).

Similarly, when evaluating programme participation, defined as attending one or more sessions of a 16-week intervention female patients were again less likely to participate. In contrast to attendance at the initial assessment patients under the age of 55 years and those with stable angina were less likely to subsequently attend the once weekly intervention programme. There were also differences in participation rates between countries with Poland, for example, having the highest rate of non-participation (43.5%) and Sweden the lowest (1.3%) when evaluating participation overall (Table 4.3.2).

Table 4.3.1: Coronary patients: comparison of patient characteristics from medical records according to attendance at initial assessment

	Eligible but no initial assessment N=528 % (n)	**Initial assessment** N=1061 % (n)	Significance*
Age			
< 50 yr	11.8% (62)	15.6% (165)	
50-59 yr	29.4% (155)	31.1% (330)	
60-69 yr	26.6% (140)	31.8% (337)	
≥ 70 yr	32.3% (170)	21.5% (228)	
mean	62.6	60.0	P<0.0001
Sex (% Female)	34.5% (182)	29.4% (312)	P=0.04
Current recruiting diagnosis			P<0.0001
Acute myocardial infarction	39.4% (207)	48.3% (512)	
Unstable angina	25.1% (132)	16.8% (178)	
Stable angina pectoris	35.6% (187)	34.9% (370)	
Elective revascularisation			
PTCA	28.6% (151)	25.7% (272)	P=0.21
CABG	3.6% (19)	6.8% (72)	P=0.01

* comparing distributions of categorical variables according to Chi-square test or the Mann-Whitney test for continuous variables

Table 4.3.2: Coronary patient characteristics by programme participation: distribution of age, sex, recruiting diagnosis and country

	Participated in programme		Did not participate	
All	**73.3%**	**(870/1187)**	**26.7%**	**(317/1187)**
Sex				
Men	71.7%	(624/870)	63.4%	(201/317)
Women	28.3%	(246/870)	36.6%	(116/317)
Age (years)				
<55	26.0%	(226/870)	40.4%	(128/317)
55-64	36.3%	(316/870)	30.6%	(97/317)
65+	37.7%	(328/870)	29.0%	(92/317)
Mean (SD)	61.2	(10.0)	58.4	(10.9)
Recruiting diagnosis				
AMI	49.5%	(431/870)	39.4%	(125/317)
Unstable angina	17.2%	(150/870)	14.8%	(47/317)
Stable angina	33.2%	(289/870)	45.7%	(145/317)
Country				
Italy	26.6%	(231/870)	4.4%	(14/317)
Spain	14.3%	(124/870)	12.9%	(41/317)
Poland	15.9%	(138/870)	43.5%	(138/317)
Sweden	15.6%	(136/870)	1.3%	(4/317)
France	10.5%	(91/870)	12.3%	(39/317)
UK	17.2%	(150/870)	25.6%	(81/317)

4.3.2: EUROACTION high risk patients

In general practice a higher proportion overall of all eligible patients participated in the intervention programme, defined as attending one or more sessions of a 1-year intervention, by comparison to the hospital arm; 82% versus 73% respectively. Unlike in the hospital intervention group where females and younger patients were less likely to participate, age and sex in primary care was similar for those who participated in the programme compared to those who did not. The key difference in participation in primary care relates to recruiting diagnosis with the greatest non-participation in the programme coming from the HeartScore group (Table 4.3.3). Interestingly these are individuals who have just found out for the first time they are at high risk of developing cardiovascular disease in the next 10 years.

Table 4.3.3: High risk patient characteristics by programme participation: distribution of age, sex, recruiting diagnosis and country

	Participated in programme		Did not participate	
All	82.1%	(947/1154)	17.9%	(207/1154)
Sex				
Men	50.7%	(480/947)	51.7%	(107/207)
Women	49.3%	(467/947)	48.3%	(100/207)
Age (years)				
<55	32.1%	(304/947)	28.5%	(59/207)
55-64	40.6%	(384/947)	42.0%	(87/207)
65+	27.4%	(259/947)	29.5%	(61/207)
Mean (SD)	60.5	(7.7)	61.6	(8.2)
Risk group*				
1	39.3%	(372/947)	57%	(118/207)
2	28.2%	(267/947)	19.3%	(40/207)
3	32.5%	(308/947)	23.7%	(49/207)
Country				
Italy	14.0%	(133/947)	16.4%	(34/207)
Spain	20.0%	(189/947)	36.7%	(76/207)
Poland	24.7%	(234/947)	10.6%	(22/207)
Denmark	9.8%	(93/947)	6.8%	(14/207)
Netherlands	18.9%	(179/947)	14.5%	(30/207)
UK	12.6%	(119/947)	15.0%	(31/207)

*Risk Group
1 = HeartScore ≥ 5%
2 = On treatment for BP-lipids
3 = Known diabetes

4.3.3 Summary

In the hospital study fewer females attended the initial assessment as well as the intervention programme itself. Coronary patients who did not attend at all were more likely to be aged 60 years of age or over. However, those patients who subsequently did not attend the weekly programme were more likely to be aged less than 55 years of age and recruited through a diagnosis of stable angina. None the less it should be noted that overall participation was extremely high at 73%.

In general practice the overall participation was even higher (82%). Age and sex were similar in those that participated in the programme to those that did not. However, people who were recruited from the HeartScore group were less likely to participate. In contrast, people who were already on treatment for raised blood pressure or abnormal lipid profiles as well as those with known diabetes were more likely to participate.

4.4: EPAF-Study: *Overall summary of the study population and recruitment*

The primary objective of the EPAF-Study in the hospital setting was to evaluate the impact at 1-year of a 16-week physiotherapy-led physical activity and supervised exercise intervention on objective physical activity participation and cardiorespiratory fitness in coronary patients compared to usual care (see Chapter 3; Section 3.1). Steps per day and fitness measures were compared in 946 coronary patients in the intervention group (661 men and 285 women; mean age 62.5 + 9.9 years) with 994 patients in usual care (695 men and 299 women; mean age 63.0 + 9.6 years). This represents 88% of all those who consented to take part in the study. Loss to follow-up was more likely in women and the elderly.

The secondary objective of the hospital study was to evaluate the effect of the physical activity and exercise intervention short term in an analysis comparing physical activity and fitness before programme commencement and on completion at 16-weeks. 883 coronary patients attended both the initial and end of programme assessments. There was practically no loss to follow-up with 99.1% attending both assessments.

Similarly the primary objective of the EPAF-Study in the general practice setting was to evaluate the impact at 1-year but this time of a 1-year nurse-led physical activity intervention on objective physical activity participation and cardiorespiratory fitness in high risk patients compared to usual care. Steps per day and fitness measures were compared in 1019 patients in the intervention group (507 men and 512 women; mean age 62.0 ± 7.6 years) with 1005 in usual care (577 men and 428 women; mean age 62.8 ± 7.3 years). Mirroring the hospital study this represented 88% of all those who consented to take part in the study. Loss to follow-up was more likely in those newly diagnosed as being at high cardiovascular risk using the HeartScore chart.

Finally, the secondary objective of the general practice study was to evaluate the changes over time in the physical activity participation and cardiorespiratory fitness from the initial assessment to 1-year in high risk patients both in the intervention and usual care groups. 91% of patients who attended the initial assessment returned for the repeat assessment at 1-year. Again loss to follow-up tended to be in the HeartScore group.

Chapter 5: Results 2

Objective physical activity participation and cardiorespiratory fitness in coronary patients

5.1: *Data completeness*

5.2: *Primary objective 1: Objective physical activity participation at 1-year*

5.3: *Primary objective 2: Cardiorespiratory fitness at 1-year*

5.4: *Secondary objective: The effect of the intervention in the short term*

5.5: *Summary*

The results for the difference in the proportion of coronary patients achieving the European Guidelines for Physical Activity (EGPA), determined by a seven day activity recall (7-DAR), in intervention versus usual care at 1-year have been previously reported (Appendix 2) and are referred to within this Chapter (as the comparator). The following reports on the results of new findings from this EPAF-Study which aimed to provide a more rigorous evaluation of the impact of the EUROACTION programme in the hospital setting in people with established coronary heart disease. Objective physical activity participation was evaluated using the Yamax Digiwalker SW-200 pedometer recording step counts and cardiorespiratory fitness was assessed using the Incremental Shuttle Walk Test (Chapter 3). The results for the effects of the EUROACTION intervention on physical activity participation (for both subjective and objective physical activity participation) and cardiorespiratory fitness are also presented.

The statistical methods used were essentially comparable to a those used in a standard meta-analysis. Whilst the overall result for all outcome measures was at a European level, the individual countries are included for reference only, as is the norm for any meta-analysis. The country data is not the focus but included to illustrate the degree of heterogeneity observed as this is important to informing later discussions.

5.1: Data completeness

As summarised by Table 5.1.1 the data was almost entirely complete for the reference outcome; the 7-DAR. The data for step counts and cardiorespiratory fitness was considerably more complete in the intervention group compared to the usual care group. Comparison of subjects with step data recorded compared to those with missing data showed no significant differences in age (p=0.40), sex (p=0.84) or the achievement of EGPA (p=0.38).

Table 5.1.1: Summary of data completion for physical activity participation and fitness in the hospital study

	COR	
	INT n=946	**UC n= 994**
Subjective Physical Activity Participation 7-DAR at 1-year	942 (99.7%)	992 (99.7%)
Objective Physical Activity Participation Steps per day at 1-year	761 (80%)	521 (52%)
Cardiorespiratory Fitness ISWT at 1-year	829 (88%)	618 (62%)

COR = coronary patients 7-DAR = 7 day activity recall ISWT = Incremental Shuttle Walk Test
INT = intervention group UC = usual care group

5.2: Objective physical activity participation – steps per day at 1-year (primary objective 1)

Extrapolated from each step log diary mean steps per day and the proportion achieving greater than 10,000 steps per day were compared, overall and by country, at 1-year using random effects modelling (Table 5.2.1 & Figure 5.2.1). The distribution of steps per day was also compared using an odds proportionate model (Table 5.2.2 & Figures 5.2.2 and 5.2.3). An Odds Ratio (OR) was calculated for each country using proportional odds models, which were subsequently combined and analysed overall by means of the same random effects meta-analysis. Here an OR greater than 1 favoured the INT arm. In all cases analyses at a European level found objective physical activity participation was significantly higher in coronary patients who had received the intervention compared to those receiving routine clinical care in usual care. There was evidence of heterogeneity between countries with Spain and France showing the greatest and least within country difference respectively.

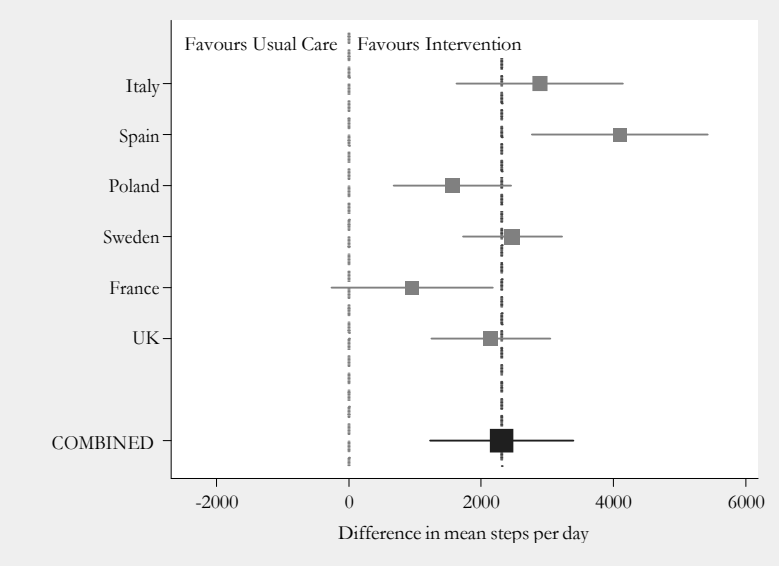
Coronary patients in INT were taking significantly more steps a day, on average an additional 2,310 steps, than their supposedly less active counterparts in UC. In absolute terms this difference equates to at least an additional mile of walking per day. The mean value in both cases fell considerably short of the 10,000 steps per day recommendation. Whilst less than a third of INT patients were achieving more than 10,000 steps per day on average this by far exceeded that seen in UC, where only one in ten were achieving this recommendation.

Table 5.2.1: Mean steps per day and proportions of coronary patients achieving ≥10,000 steps per day at 1 year – INT *vs* UC-ALL

	INT	UC-ALL	Difference (95% CI)
Steps per day			
Number	761	521	
Mean (SD)	7893 (3808)	5684 (3368)	+2310 (1226 to 3394) , **P=0.003***
Mean steps per day >10,000			
% (n)	28.0% (213/761)	9.2% (48/521)	+18.1% (6.1% to 30.1%) , **P=0.01***

** According to random effects modelling (REML estimation)*

Figure 5.2.1: Difference in the mean steps per day in coronary patients at 1 year – INT *vs* UC-ALL, by country



The distribution for mean steps in INT and UC, using the Tudor-Locke classification system (Tutor-Locke & Bassett, 2004) (Figure 5.4.2), was significantly different between INT and UC with the former presenting a more active lifestyle (Figures 5.2.2 & 5.2.3 and Table 5.2.2). Finally, when analysing the odds ratio by country (Figure 5.2.3) there was a significant difference in the distribution for steps per day across all six countries.

Figure 5.2.2: Proportions (%) of patients in each category: < 5000; 5000 - < 7,500; 7,500 - < 10,000 and ≥ 10,000 steps per day – INT *vs* UC-ALL

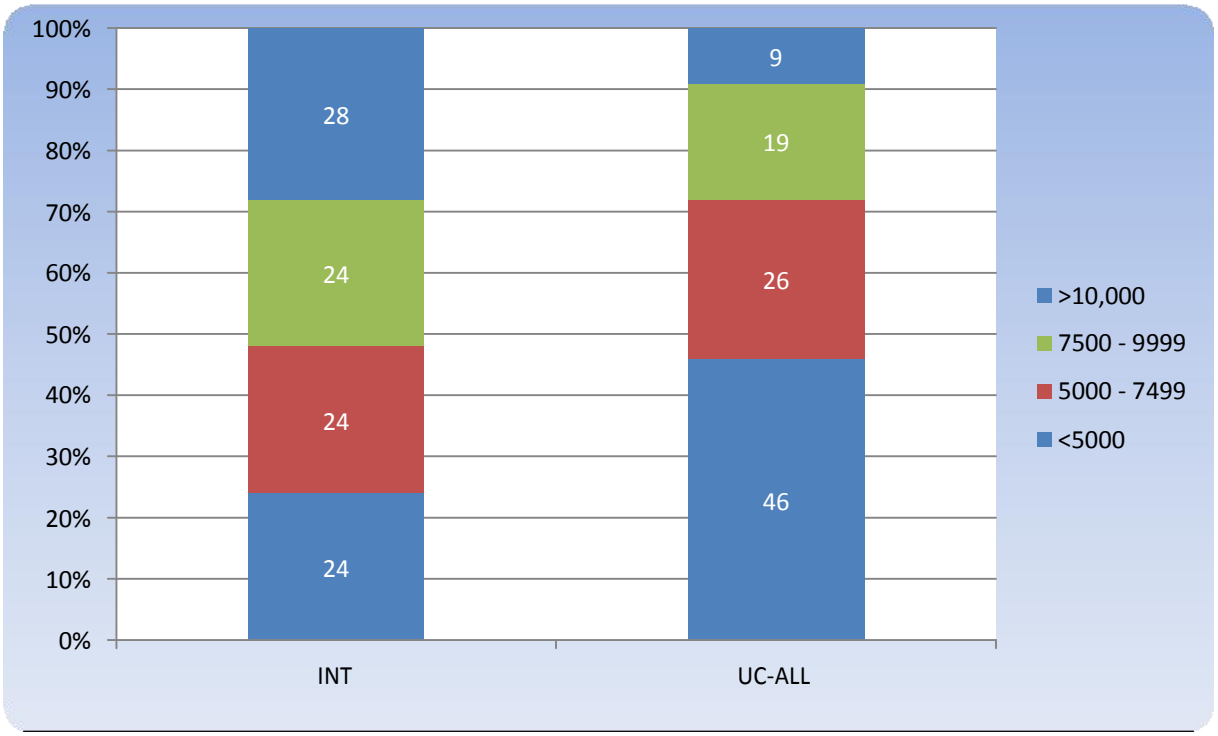
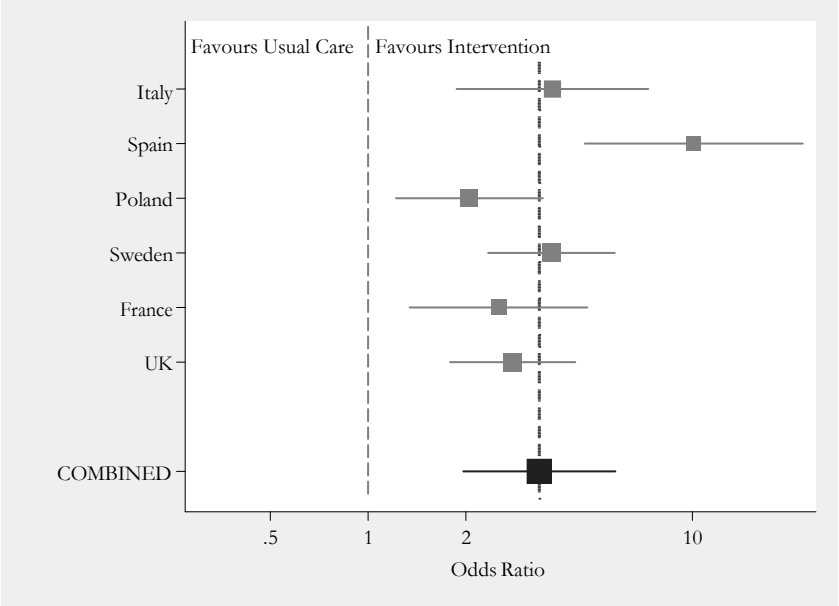


Table 5.2.2: Proportions (%) of patients in each category: < 5000; 5000 - < 7,500; 7,500 - < 10,000 and ≥ 10,000 steps per day – INT *vs* UC-ALL

	INT		UC-ALL	
All patients				
<5,000	23.7%	(180/761)	45.7%	(238/521)
5,000-7,490	24.1%	(183/761)	26.1%	(136/521)
7,500-9,999	24.3%	(185/761)	19.0%	(99/521)
10,000+	28.0%	(213/761)	9.2%	(48/521)
Odds Ratio	**3.37 (1.97 to 5.79) , P=0.002***			

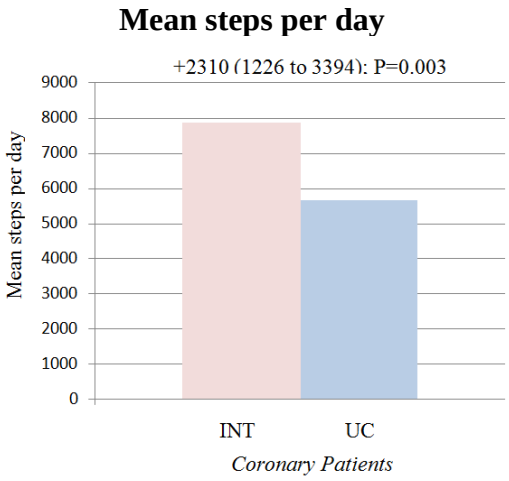
**Odds ratio from proportional odds model calculated for each country and combined using a random effects meta-analysis (REML estimation). An OR>1 favours the Intervention arm.*

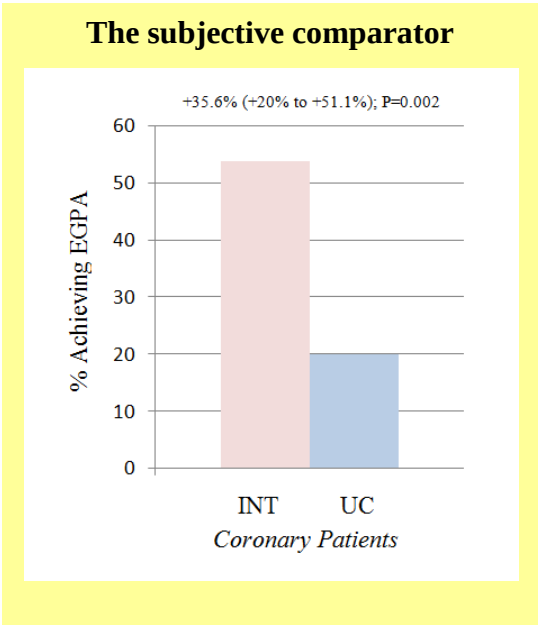
Figure 5.2.3: Odds Ratio for step counter categories – INT *vs* UC-ALL, by country

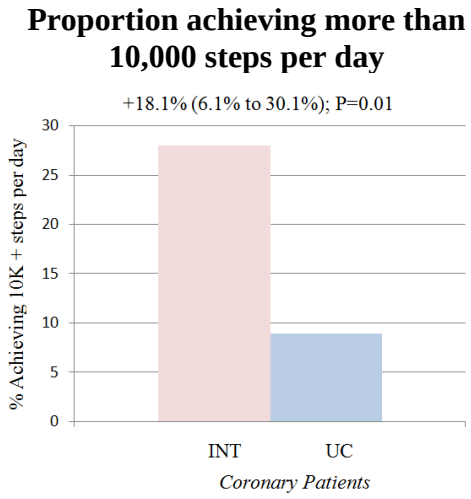


The findings for the objective physical activity measures used in this study support the subjective findings previously reported by the main EUROACTION study (Figure 5.2.4). The EUROACTION intervention significantly increased self-reported participation in physical activity and this was objectively supported by the same direction of change being observed for steps per day. However, whilst increases in physical activity participation are cardioprotective it is well recognised that gains in physical fitness offer considerable protection. These increases in physical activity participation would be far more meaningful if they translate to changes in cardiorespiratory fitness. These results now follow in Section 5.3.

Figure 5.2.4: Physical activity participation - *objective* vs *subjective* measures at 1-year







5.3: The impact of the EUROACTION programme on cardiorespiratory fitness in coronary patients (primary objective 2)

The Incremental Shuttle Walk Test (ISWT) is described in detail in Chapter 3 (Methodology). Using the same random effects modelling, to account for within and between country differences, the metres scored were compared at 1-year, INT *vs* UC-ALL.

At 1-year a total of 1447 coronary patients had performed the ISWT, equating to 88% (829/946) of all INT patients and 62% (618/994) of all in UC. There were major differences in participation both between and within countries (Table 5.3.1). The most striking difference was seen in Spain, where patients in UC performed much better on the ISWT than patients in INT (Table 5.3.2). However, 96% of patients in INT participated in the ISWT while only 37% from UC participated. On the other hand the only two centres where results were in favour of INT were Sweden and the UK; noting these were also the only two centres where participation in the ISWT exceeded 80% in both the INT and UC centres. Overall, whilst INT scored on average 54 metres in the ISWT at 1-year compared to UC and whilst this difference is clinically meaningful, it was not statistically significant (Table 5.3.2).

Table 5.3.1: Rates of participation in the ISWT at 1-year –INT *vs* UC

	Spain	**Italy**	**France**	**Poland**	**Sweden**	**UK**
INT n (%)	136 (96%)	201 (93%)	73 (86%)	142 (72%)	124 (91%)	153 (90%)
UC-ALL n (%)	69 (37%)	87 (58%)	104 (60%)	114 (60%)	125 (81%)	119 (86%)
Difference	+59%	+35%	+26%	+12%	+10%	+4%

Table 5.3.2: Difference in metres scored (ISWT) at 1-year – INT *vs* UC-ALL

	INT		**UC-ALL**		**Difference (95% CI)**
Country	Mean metres	(SD)	Mean metres	(SD)	
Spain	244.5	(150.4)	357.9	(107.3)	
Italy	516.6	(201.2)	196.4	(87.0)	
France	416.6	(121.9)	434.4	(164.0)	
Poland	315.0	(138.3)	336.1	(173.7)	
Sweden	506.1	(162.0)	447.0	(128.3)	
UK	454.7	(180.5)	355.3	(166.2)	
COMBINED	**415.5**	**(196.1)**	**369.0**	**(171.2)**	**+54.0m (-102.8 to +211.0) P=0.42**

In summary, at face value there was no difference in fitness, expressed as metres scored in the ISWT, between INT and UC. However, the ISWT results were difficult to interpret and raised many discussion points, which will be explored more fully later.

5.4: The effect of the 16-week EUROACTION intervention on physical activity participation and cardiorespiratory fitness (secondary objective)

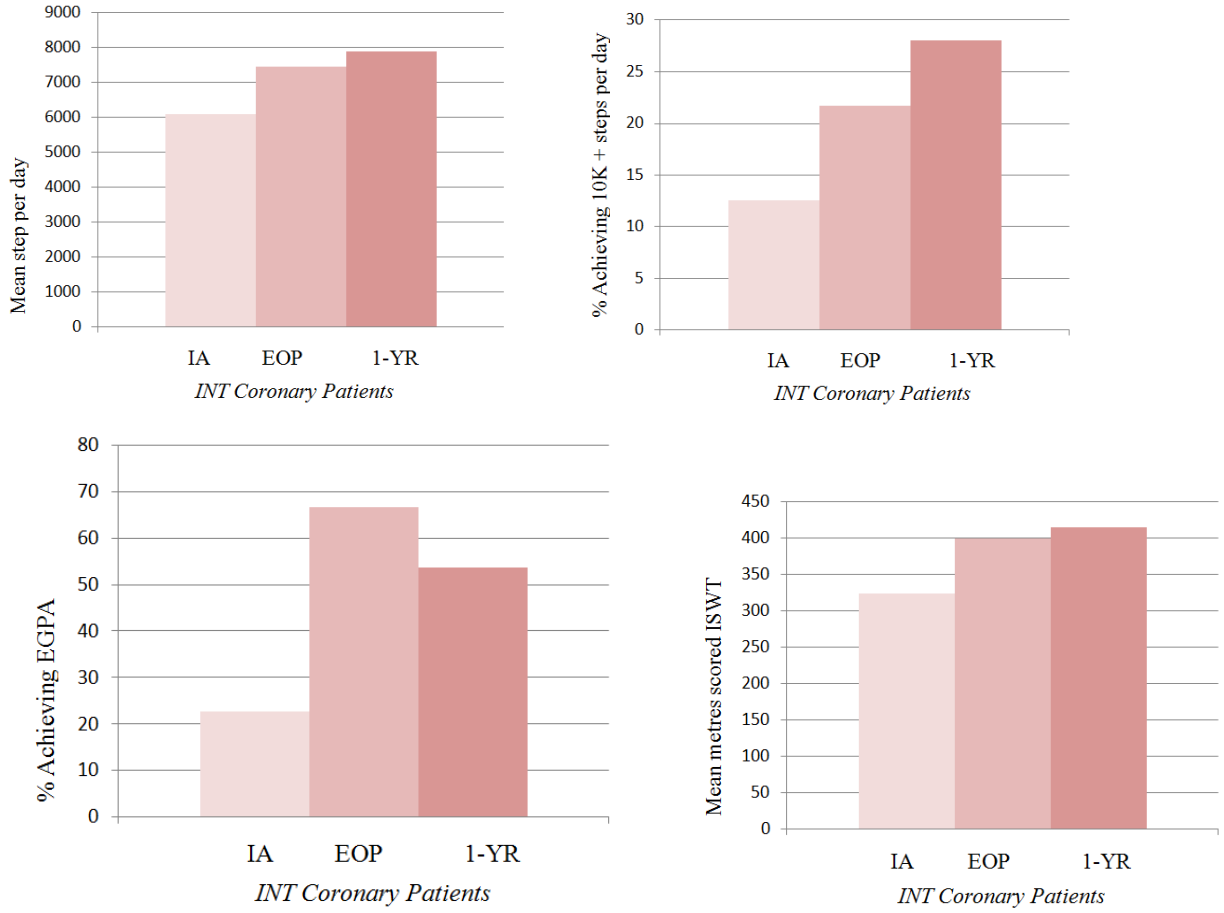
As described in the methodology (Chapter 3) the hospital intervention comprised of a 16-week intervention with a follow-up 1-year after the initial assessment. In being able to discuss the results at 1-year more fully there needs to be some appreciation of the effects of the programme in the short term. 883 (99.1%) of coronary patients attended both the initial and end of programme assessment at 16-weeks highlighting that there was almost no loss to follow-up for this time-frame. Across all parameters for physical activity participation and cardiorespiratory fitness a significant improvement was seen (Table 5.4.1).

Table 5.4.1: The effects of the 16-week EUROACTION intervention in physical activity participation and cardiorespiratory fitness

Proportion achieving the EGPA (subjective measure of physical activity participation)	
Baseline 16 weeks Δ (95% CI) Significance	22.7% 66.8% 44.1% (+ 40.4% to +47.8%) P<0.0001
Mean steps per day (objective measure of physical activity participation)	
Baseline 16 weeks Δ (95% CI) Significance	6098.3 steps 7460.4 steps 1362.1 steps (+1127.2 to +1597.0) P<0.0001
Proportion achieving ≥ 10,000 steps per day	
Baseline 16 weeks Δ (95% CI) Significance	12.6% 21.7% 9.1% (5.9%/12.2%) P<0.0001
Cardiorespiratory Fitness (metres scored in the Shuttle Walk Test)	
Baseline 16 weeks Δ (95% CI) Significance	324.2m 400.0m 75.8m (+67.4m to +84.2m) P<0.0001

The results also highlight the effects of the 16-week programme were not lost at 1-year (Figure 5.4.1). In all cases, bar self-reported activity, the benefits were at least maintained with evidence of further improvements seen at 1-year.

Figure 5.4.1: Short term (16 weeks) and long term (1-year) changes in physical activity participation and cardiorespiratory fitness in coronary patients receiving the EUROACTION intervention



5.5: Summary of physical activity results in coronary patients

Overall the results show that the EUROACTION intervention was effective in raising physical activity participation in coronary patients, as reflected by self-reported activity and objectively by average steps per day. These changes did not necessarily have an impact on physical fitness. There was evidence of considerable heterogeneity both between and within countries across the results.

Chapter 6: Results 3

Objective physical activity participation and cardiorespiratory fitness in asymptomatic individuals at high risk of developing cardiovascular disease

This Chapter reports on the results for the general practice part of the EUROACTION Physical Activity and Fitness Study (EPAF-Study). As with the Chapter 5, the previously published results for self-reported physical activity participation from the main trial (Wood et al., 2008) will be referred to as the comparator. The EPAF-Study in general practice evaluates the impact of the EUROACTION physical activity and exercise intervention on objective physical activity participation using the Yamax Digiwalker SW-200 pedometer and cardiorespiratory fitness as measured by the Chester Step Test (Chapter 3). The primary outcome was the difference in these parameters between intervention (INT) and usual care (UC) at 1-year. The secondary outcome of change over time in these measures in both the intervention and usual care groups and the difference in this change is also reported.

These results will be presented by intervention and usual care group overall as well as by each of the three diagnostic sub-groups: i. Individuals without known diabetes and not on treatment for either hypertension or hypercholesterolemia presenting with a HeartScore>5%. In other words apparently healthy individuals newly diagnosed as being at high risk of developing CVD over the next 10-years; ii. HRI already on treatment for either hypertension or hypercholesterolemia for less than two years; and iii. People with known diabetes, either newly diagnosed or for less than three years.

As with the previous Chapter, the reader should note the results for the EPAF-Study are at a European level. The "by country" data are included within tables and figures, as is standard for any meta-analysis, to provide information in relation to the degree of heterogeneity experienced.

6.1: Data completeness

As summarised by Table 6.1.1 the data was almost entirely complete for the reference outcome; the 7-DAR. The data for step counts at 1-year was reasonably complete (87% INT; 94% UC). Cardiorespiratory fitness was considerably more complete in the usual care group (81%) compared to the intervention group (65%). Comparison of subjects with fitness data in intervention compared to those with missing data showed no significant differences for age ($p=0.56$), sex ($p=0.70$) or the achievement of EGPA ($p=0.14$). For the comparison of the difference in change over 1-year, this used a random subsample of the population and for all parameters data completion rates were high.

Table 6.1.1: Summary of data completion for physical activity participation and fitness in the general practice study

	HRI	
	INT n=1019	**UC n= 994**
Subjective Physical Activity Participation 7-DAR at 1-year	1018 (99.9%)	1003 (99.8%)
Objective Physical Activity Participation Steps per day at 1-year [(1)]	887 (87%)	944 (94%)
Cardiorespiratory Fitness CST at 1-year [(1)]	666 (65%)	810 (81%)
Subjective Physical Activity Participation Change in 7-DAR (IA to 1-year) [(2)]	955 (94%)	233 (93%)*
Objective Physical Activity Participation Change in steps per day (IA to 1-year) [(2)]	867 (85%)	226 (90%)*
Cardiorespiratory Fitness Change I CST (IA to 1-year) [(2)]	182 (91%) ~	188 (94%) ~

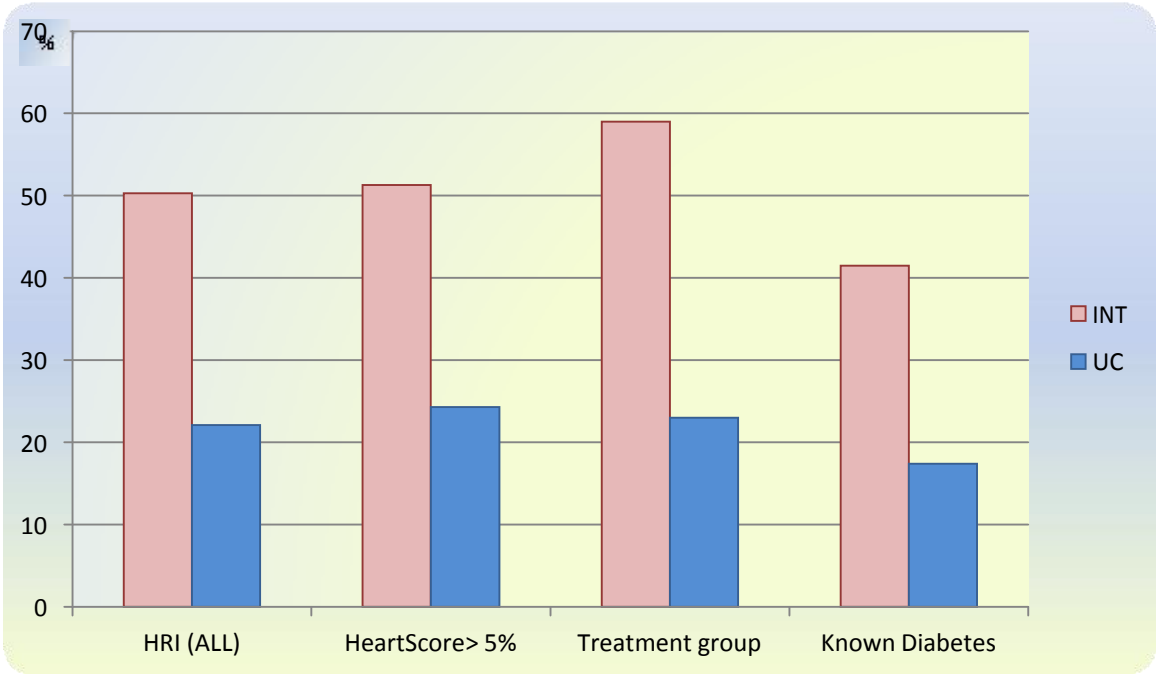
HRI = high risk individuals 7-DAR = 7 day activity recall CST = Chester Step Test
IA = Initial assessment INT = intervention group UC = usual care group
[(1)] Primary outcome [(2)] Secondary outcome
*Random subsample of 25% of all UC ~ Random subsample of 200 patients

6.2: Objective physical activity participation – steps per day at 1-year (primary objective 1)

The main EUROACTION trial found significant improvements in self-reported physical activity participation in HRI; overall and by diagnostic group (Figure 6.2.1) (Wood et al., 2008). This result used a subjective measure and sets the scene for the EPAF-Study which used the more objective measure of step counts to evaluate the impact of the physical activity and exercise intervention.

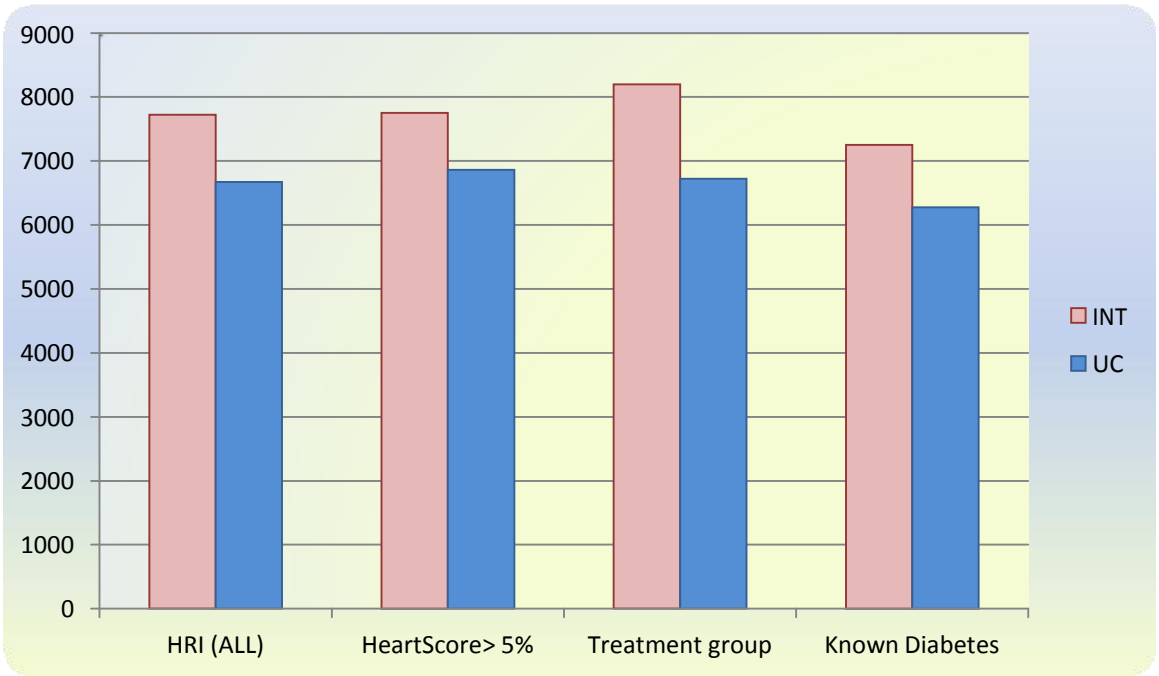
The results of the random effects meta-analysis suggest that there was no evidence of a statistically significantly difference in mean steps per day between INT and UC at 1-year overall and across all three diagnostic groups (Figure 6.2.2). There is however a clear trend in favour of the intervention and the magnitude exceeds the minimum clinically important difference meaningful difference in special populations of 775 steps (Tudor-Locket and Bassett, 2004).

Figure 6.2.1: Proportions of HRI achieving the European Guidelines for Physical Activity (EGPA) at 1-Year (INT v UC-ALL and by diagnostic group).



HRI (ALL)	HeartScore> 5%	Treatment group	Known Diabetes
+29.4% (+10.5% to +48.2%) **P=0.01**	+26.1% (+6.7% to +45.5%) **P=0.02**	+34.8% (+14.9% to +54.7%) **P=0.006**	+27.5% (+8.1% to +46.9%) **P=0.02**

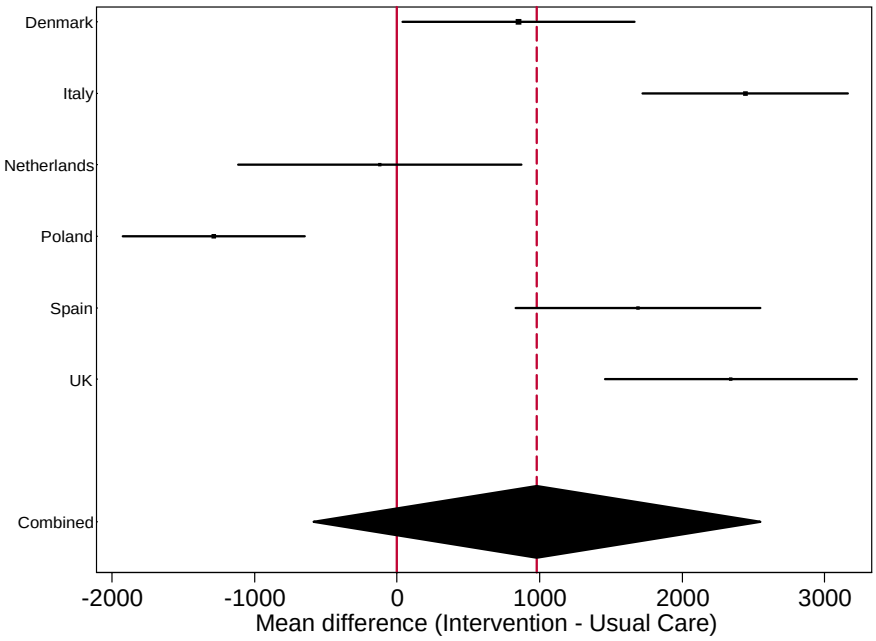
Figure 6.2.2: Mean steps per day in HRI at 1-Year (INT v UC-ALL and by diagnostic group).



HRI (ALL)	HeartScore> 5%	Treatment group	Known Diabetes
+982.0 (-569.4 to +2533.4) **P=0.17**	+710.8 (-1013.5 to +2435.1) **P=0.34**	+1232.8 (-528.5 to +2994.1) **P=0.34**	+1225.4 (-674.8 to +3125.6) **P=0.16**

Whilst the EPAF-Study"s objectives were to report outcomes for objective physical activity participation and cardiorespiratory fitness at a European level it is important to note there was considerable heterogeneity both within and between countries (Figure 6.2.3). This is an excellent example, which will be discussed in detail later, demonstrating the impact of clustering of data within countries and how this can lead to a substantial loss in statistical power.

Figure 6.2.3: A Forest plot of the difference in the mean steps per day in HRI at 1 year – INT *vs* UC-ALL, by country



Given the relatively low mean values for steps per day it was unsurprisingly that very few HRI (26% INT; 19% UC) were achieving more than 10,000 steps per day at 1-year (Table 6.2.1). The by country data, whilst not the primary focus, revealed enormous variation.

Table 6.2.1: Proportion of HRI with mean steps per day ≥10,000, by country and overall, at 1 year – INT *vs* UC-ALL

	INTERVENTION % (n)	**USUAL CARE** % (n)	**Difference (95% CI)**
Denmark	19.0% (18/95)	13.1% (18/137)	
Italy	24.5% (38/155)	9.8% (18/183)	
Netherlands	20.1% (31/154)	18.5% (20/108)	
Poland	27.9% (65/233)	42.8% (68/159)	
Spain	33.3% (56/168)	17.2% (32/186)	
UK	26.8% (22/82)	15.8% (27/171)	
ALL	**25.9% (230/887)**	**19.4% (183/944)**	+5.8% (-6.2% to +17.9%) **P=0.27***

** According to random effects modelling (REML estimation)*

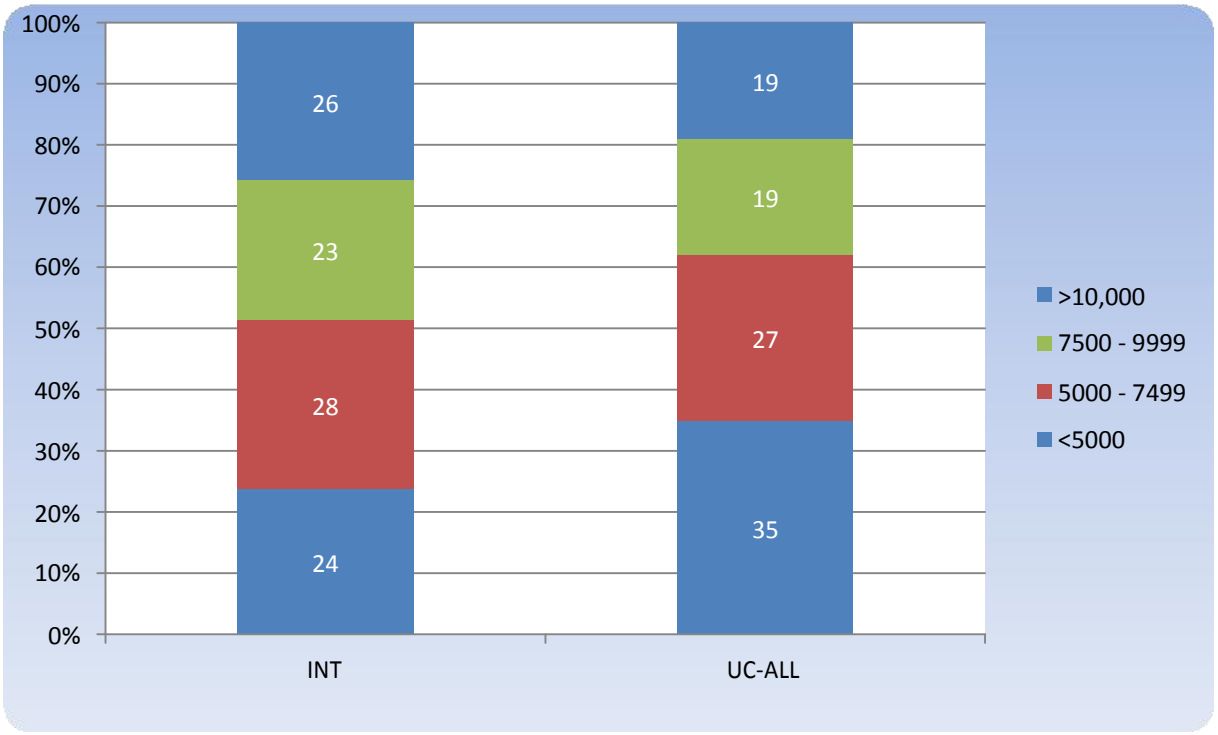
An odds ratio (OR) was calculated for each country using proportional odds models and then combined in a random effects meta-analysis (REML estimation) to analyse the distribution of steps per day. Here an OR greater than 1 favoured the INT arm Whilst the overall difference in the distribution of mean steps per day at 1-year was not statistically significant there was a clear trend in favour of INT (Table 6.2.2 & Figure 6.2.4).

Table 6.2.2: Proportions (%) of patients in each category: < 5000; 5000 - < 7,500; 7,500 - < 10,000 and ≥ 10,000 steps per day – INT *vs* UC-ALL

	INT		**UC-ALL**	
All patients	%	(n)	%	(n)
<5,000	24.0%	(213/887)	35.1%	(331/944)
5,000-7,490	27.5%	(244/887)	26.5%	(250/944)
7,500-9,999	22.6%	(200/887)	19.1%	(180/944)
10,000+	25.9%	(230/887)	19.4%	(183/944)
Odds Ratio	**1.56 (0.66 to 3.71) , P=0.24***			

**Odds ratio from proportional odds model calculated for each country and combined using a random effects meta-analysis (REML estimation). An OR>1 favours the Intervention arm.*

Figure 6.2.4: Proportions (%) of patients in each category: < 5000; 5000 - < 7,500; 7,500 - < 10,000 and ≥ 10,000 steps per day – INT *vs* UC-ALL



In summary, the results for a comparison of steps per day, both mean steps and distribution, at 1-year were consistent with the null hypothesis. However, the trends are all very clearly in favour of the intervention and the absolute magnitude of difference achieved represents favourable improvements that are clinically meaningful.

6.3: The impact of the EUROACTION programme on cardiorespiratory fitness in HRI (primary objective 2)

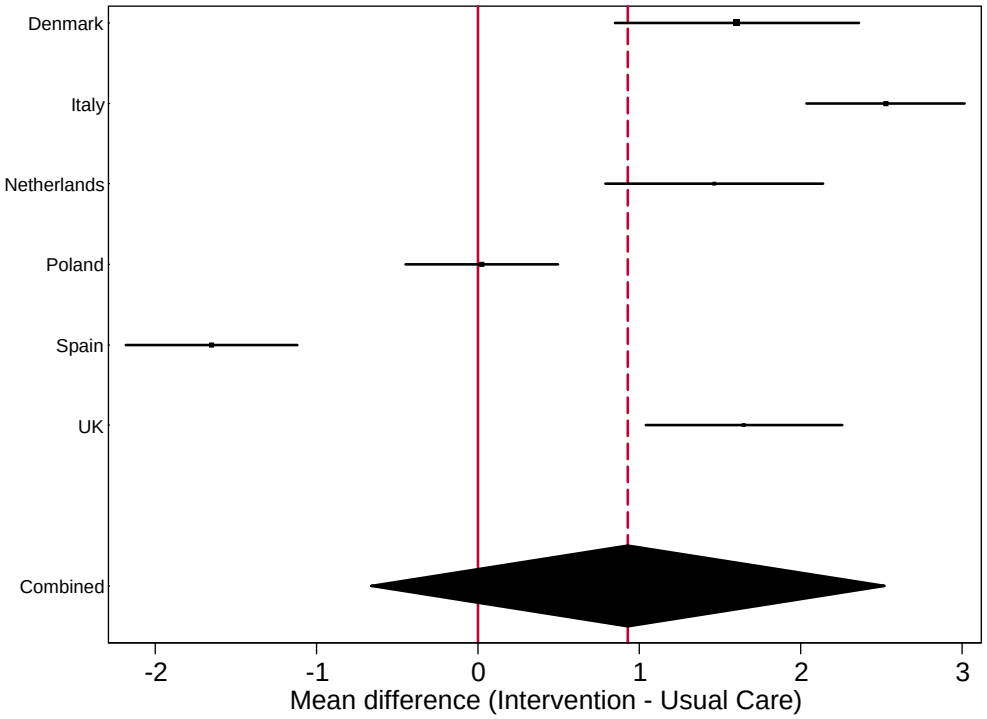
The CST is described in detail in Chapter 3 (Methodology). Using the same random effects modelling, the time achieved on the CST was compared at 1-year in INT *vs* UC-ALL. Post-hoc analyses by diagnostic group were also carried out. At 1-year a total of 1476 HRI performed the CST (666 INT and 810 UC). Similar to findings for mean steps per day, there was no evidence of a statistically significant difference overall in cardiorespiratory fitness between groups at a European level (Table 6.3.1). As illustrated for completeness there was evidence of heterogeneity and evidence that the intervention was effective in the majority of within country analyses (Figure 6.3.1).

Table 6.3.1: Mean minutes scored for Chester Step Test at 1-year – INT *vs* UC.

Country	**INTERVENTION n=666** Mean (SD)	**USUAL CARE n=810** Mean (SD)	Difference (95% CI) P-value*
Denmark	8.82 (1.76)	7.28 (2.73)	
Italy	7.50 (2.08)	4.98 (2.32)	
Netherlands	8.09 (2.43)	6.63 (2.74)	
Poland	6.98 (2.00)	6.96 (1.72)	
Spain	5.45 (2.24)	7.11 (2.21)	
UK	7.15 (1.91)	5.50 (2.35)	
ALL	**7.16 (2.37)**	**6.25 (2.51)**	+0.93 (-0.62 to +2.48) **P=0.18**

* According to random effects modelling (REML estimation)

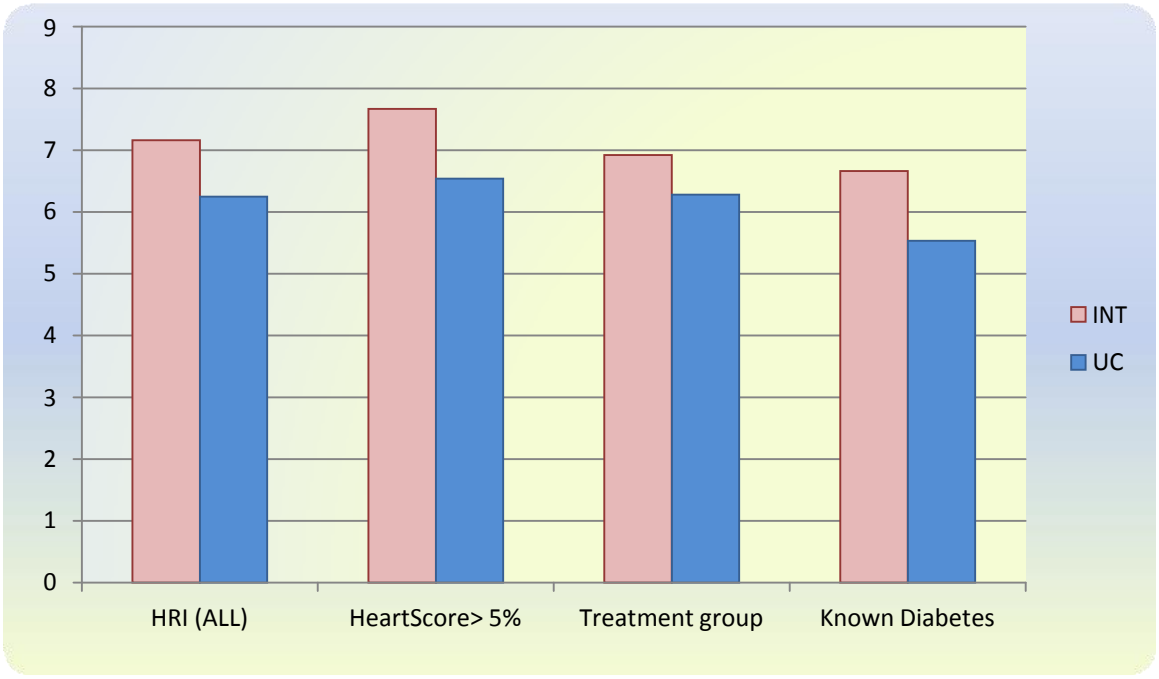
Figure 6.3.1: Forest plot of the mean minutes scored for Chester Step Test at 1-year – INT *vs* UC.



Post-hoc analyses also revealed the same pattern of results irrespective of diagnostic group (Figure 6.3.2). All three groups revealed a trend in physical fitness in favour of INT but this difference did not reach significance at the 5% level. Within each of the six counties heterogeneity was once again apparent and in agreement with the main analysis for cardiorespiratory fitness.

Essentially, the results for the EPAF-Study‟s primary outcome in relation to cardiorespiratory fitness were consistent with the null hypothesis. However, the trends were again all very clearly in favour of the intervention. There is no data available in relation to the minimum clinically important difference in time achieved in the CST but it should be noted before drawing strong conclusions that there was sizable heterogeneity observed between and within countries.

Figure 6.3.2: Cardiorespiratory fitness at 1-Year (INT v UC-ALL and by diagnostic group) (presented as minutes achieved in the CST).



+0.93 (-0.62 to +2.48) **P=0.18**	+0.93 (-0.67 to +2.52) **P=0.20**	+0.79 (-0.91 to +2.49) **P=0.29**	+1.22 (-0.91 to +3.36) **P=0.20**

6.44: The difference in the change from the initial assessment to1-year in physical activity participation and cardiorespiratory fitness in HRI (secondary objective)

Given the heterogeneity observed within a country and between countries, these next and final analyses provide a valuable „more stable" evaluation of the effectiveness of the physical activity and exercise intervention in HRI. In general practice physical activity participation (both subjectively and objectively measured) and cardiorespiratory fitness were assessed in both INT and UC at baseline and at 1-year. These analyses importantly overcome the issue of heterogeneity as they evaluate the "*difference* in the *difference in change* over 1-year" as opposed to reporting the absolute difference between INT and IC at 1-year, which does not account for any differences between the two populations at baseline or possible systematic errors.

In relation to physical activity participation, this 1-year intervention almost doubled the proportion of HRI achieving the EGPA and this change was statistically significant. In UC, over the period of a year the proportion achieving the physical activity targets significantly fell (Figure 6.4.1). An overall difference of 33% was observed between the changes over 1-year in favour of the INT (P=0.01) in the subjective measurement of physical activity participation. The results for the difference in change over time for objectively measured physical activity participation fully concurs in the INT group highlighting that these self-reported increases were substantiated by a simultaneous increase in daily step counts. In UC, there was no significant difference observed in the change in steps between the initial assessment and 1-year follow-up (Figure 6.4.2). The difference in the change over time between INT and UC equated to almost 900 steps which may be clinically meaningful but this difference was not significant at the 5% level.

The results for physical activity participation demonstrate that the physical activity intervention delivered in those assigned to the intervention group in general practice was effective. The practice nurses effectively increased physical activity participation (both subjectively and objectively measured). In evaluating the achievements in physical activity for routine care there was no significant change in the objective physical activity participation. The difference in the change over time between INT and UC was only statistically significant for subjectively measured physical activity participation.

Figure 6.4.1: Changes over 1-year and difference in change in achieving the EGPA in HRI (subjective measure for physical activity participation)

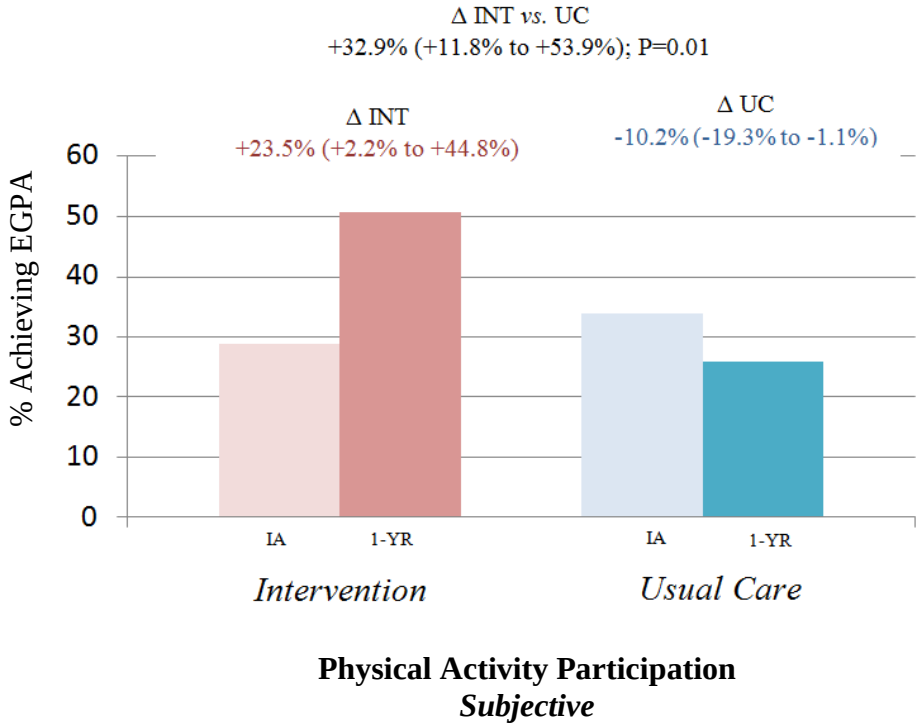
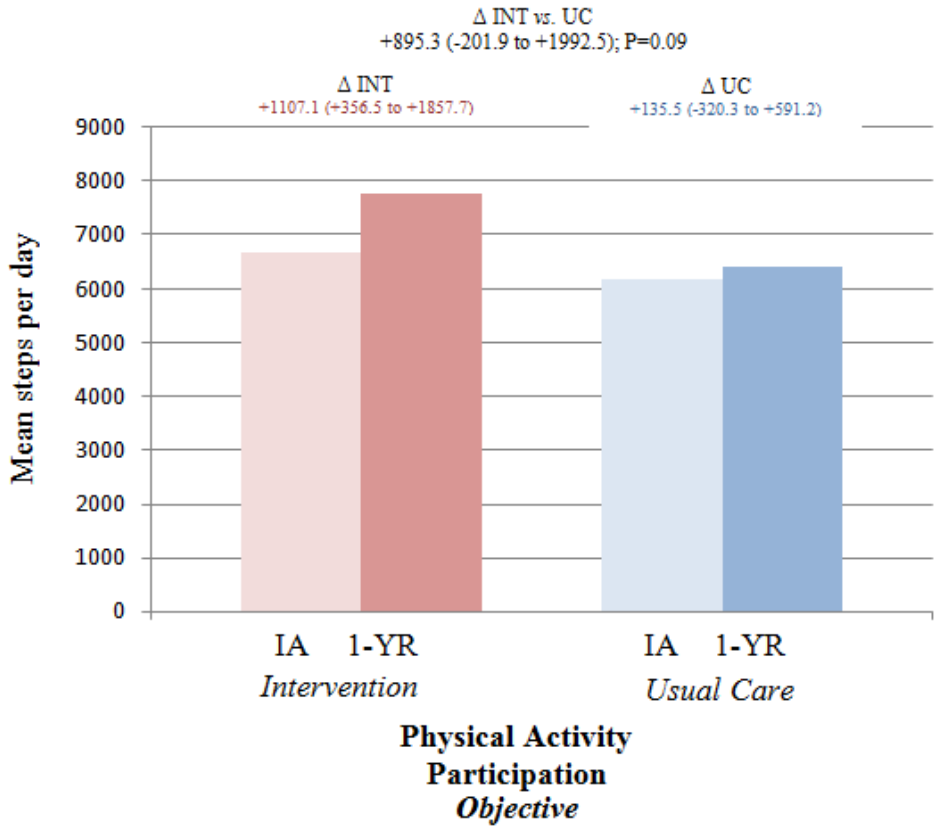
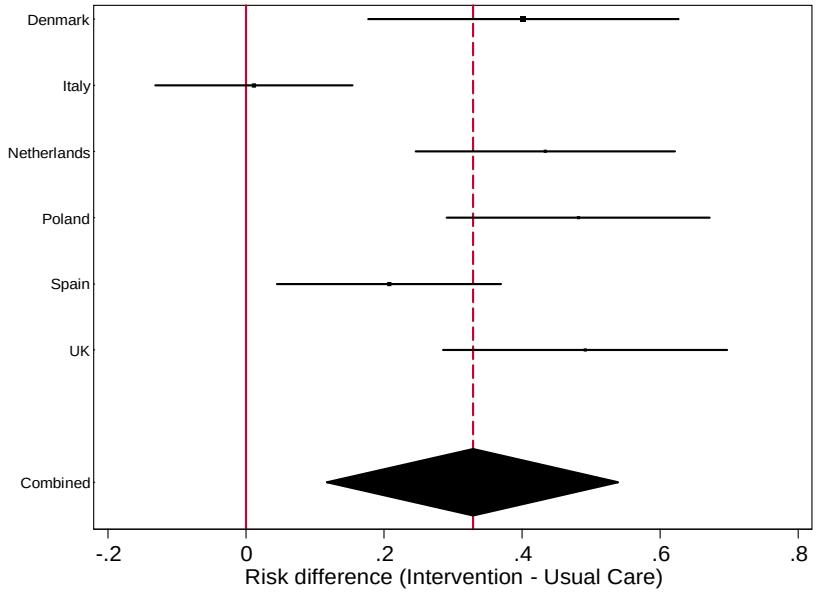


Figure 6.4.2: Changes over 1-year and difference in change in mean steps per day in HRI (objective measure for physical activity participation).

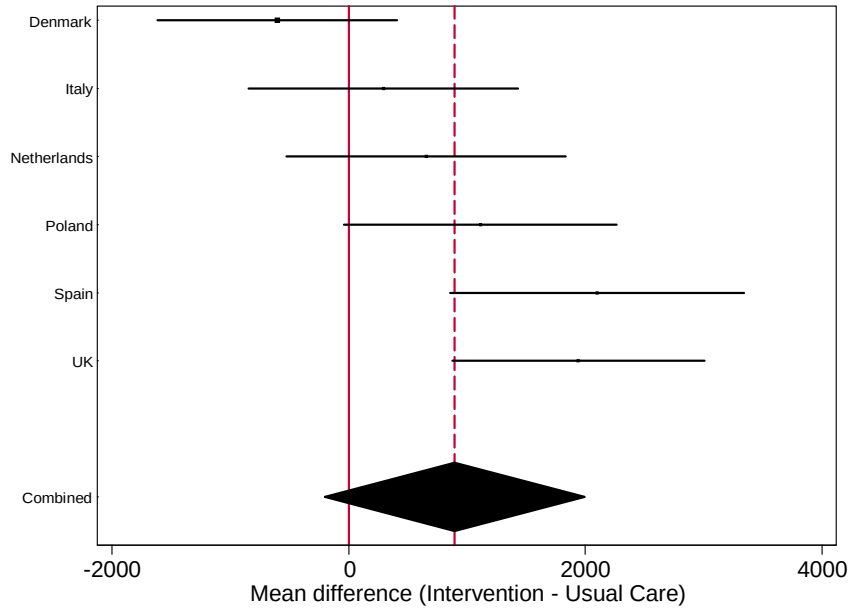


As with all results for the EPAF-Study the focus is the outcome at a European level. However as these analyses were essentially a meta-analysis, the Forest plots are presented in Figure 6.4.3. The heterogeneity observed is important to later discussions regarding loss of statistical power.

Figure 6.4.3: Forest plot of difference in change in the proportion of HRI's achieving the EGPA over 1-year and mean steps per day– INT *vs* UC-SS, by country



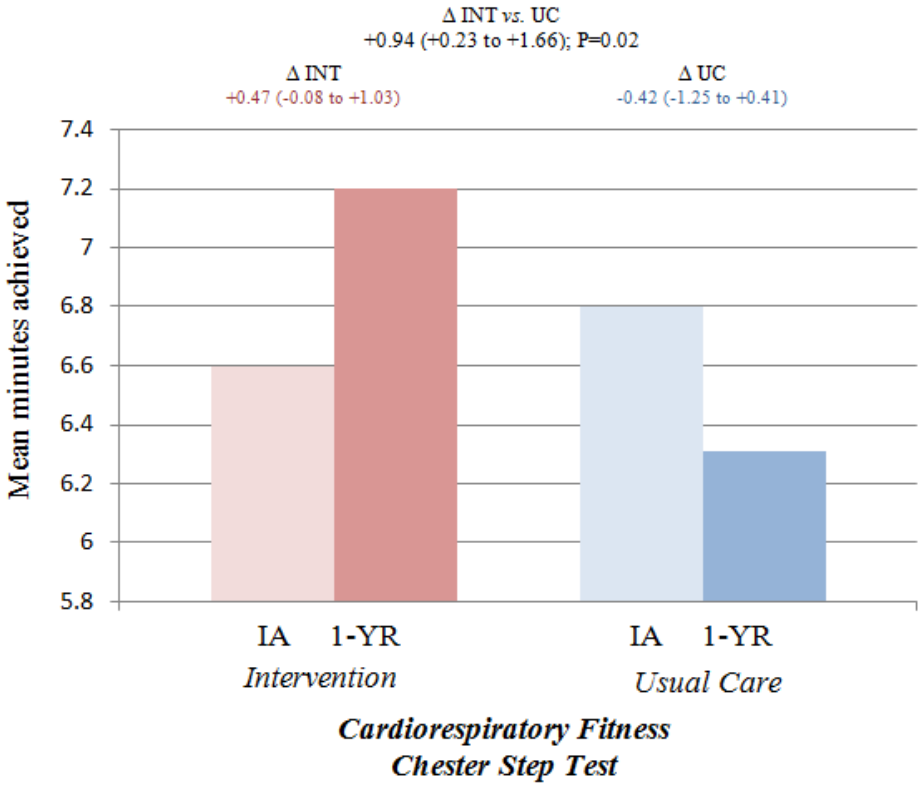
a. ***Subjective*** physical activity participation



b. ***Objective*** physical activity participation

In relation to cardiorespiratory fitness, the trends for the change in fitness mirrored those for self-reported physical activity. Whilst increased performance time was achieved in the CST in INT and the reverse seen in UC, the change within each group over time was not statistically significant. However, the difference in the change in cardiorespiratory fitness over 1-year observed between INT and UC was statistically significant indicating that the EUROACTION intervention was more effective than routine clinical practice at improving aerobic capacity (Figure 6.4.4).

Figure 6.4.4: Changes over 1-year in cardiorespiratory fitness.



6.5: Summary of physical activity results in HRI in general practice

The main EUROACTION trial reported strong evidence for the value of the EUROACTION physical activity intervention in general practice (Wood et al., 2008). However, this was entirely based on a self-reported subjective outcome of physical activity participation in a comparison of INT and UC at 1-year. In the EPAF-Study, trends for objectively measured physical activity participation and cardiorespiratory fitness were consistently in favour of the INT but unlike the subjective measures previously reported, neither outcome was found to be statistically significant at 1-year. However, it should be noted that there was enormous heterogeneity observed both within and between countries, impacting greatly on statistical power, and the absolute differences found between INT and UC did represent clinically meaningful results.

The change in physical activity and cardiorespiratory fitness over the 1-year offers a more robust evaluation. Whilst the differences over time in subjective physical activity participation suggest the EUROACTION was highly effective, objective measures do not support the same magnitude of effect. On the other hand, significant differences were seen in the change in cardiorespiratory fitness over 1 year, which would suggest this nurse-led intervention was more effective in increasing aerobic capacity than current routine clinical practice.

Chapter 7: Discussion

7.1*:* *Study strengths*

7.2*:* *Study limitations and sources of bias*

7.3 *The effectiveness of the EUROACTION programme in raising physical activity participation and cardiorespiratory fitness at 1-year*

7.4: *Changes over time in physical activity participation and cardiorespiratory fitness*

7.5*:* *Other important findings to inform preventive cardiology practice*

7.6: *Future research recommendations*

The European Action on Secondary and Primary prevention through Intervention to Reduce Events (EUROASPIRE) surveys showed that CVD prevention in routine clinical practice has remained inadequate over the past decade (Kotseva et al., 2010; Kotseva et al., 2009a; Kotseva et al., 2009b; EUROASPIRE II Study Group, 2001a; EUROASPIRE II Study Group, 2001b; EUROASPIRE Study Group, 1997). Longitudinally, the EUROASPIRE surveys demonstrate no improvements in physical activity participation; with only 30% of adults achieving the physical activity target. Consequently there is an urgent need to identify solutions, through high quality research, to translate evidence-based physical activity CVD prevention guidelines into clinical practice.

The EUROACTION trial spanned eight countries and 24 hospital and general practice centres, in a cluster randomised controlled trial (Wood et al., 2004). Publication of the main results show that a protocol driven multifactorial risk modification programme, coupled with the support and involvement of a patient‘s partner and family, can yield significant lifestyle improvements and risk factor reductions in coronary patients and patients at risk of developing cardiovascular disease. As published in the Lancet, significant improvements were observed in patients and their partners in key lifestyle and other risk factors: diet, physical activity, central obesity, blood pressure, cholesterol and glucose.

The EUROACTION programme has the potential to revolutionise the approach to cardiovascular disease (CVD) prevention in Europe. However, a single outcome was used for physical activity; essentially a subjective assessment of physical activity participation by means of a seven day activity recall. It is widely accepted that self-reported activity is prone to systematic errors (Chapter 2) and consequently the EUROACTION trial in isolation cannot draw any strong conclusions with this regard. This study, entitled the EUROACTION physical Activity and Fitness Study (EPAF-Study) has provided a far more robust evaluation of the EUROACTION programme which, given the above, offers a valuable contribution to the research community. This Chapter will firstly discuss the strengths and limitations of the EPAF-Study in order to provide the necessary context before interpreting the study findings in relation to this objective evaluation of the impact of the EUROACTION programme on physical activity participation and cardiorespiratory fitness in coronary patients and individuals with a high multifactorial risk for developing cardiovascular disease. These discussions aspire to better inform service providers whether this approach to care delivery offers any value (or not) above that currently being delivered in routine clinical care.

7.1: Study strengths

The EUROACTION programme incorporated several important principles that make the findings of this EPAF-Study generalisable to current clinical practice. First, the programme was intentionally set up in busy general hospitals and general practices, outside specialist cardiac rehabilitation centres, to provide a service for all coronary and high-risk patients in routine clinical practice. The EUROACTION programme did not use specialised hospital or community facilities; simple equipment was used for the supervised exercise sessions so that the exercises could be replicated at home. As a consequence EUROACTION can be set up in any hospital or general practice without dedicated facilities.

Secondly, EUROACTION was inclusive because it addressed all the high-priority patient groups as defined in the guidelines, including those most recently published (Wood et al., 1998; De Backer et al., 2003; Perk et al., 2012). The programme made no distinction between symptomatic coronary disease (secondary prevention) and those at high risk (primary prevention). All these patients are at high risk of cardiovascular disease and need professional support to achieve the same lifestyle and risk factor targets. This approach was employed in the belief that integration of the diagnosis and management of patients with continued preventive care in the same medical facility is likely to result in increased and sustained participation. These findings highlight that this model of care is applicable to current practice and it is feasible to reconfigure existing services to provide an integrated care approach.

Thirdly, participation rates were excellent increasing the generalisability of findings to the population with established CVD and those at high risk of developing disease more widely. In the EUROASPIRE survey (Kotseva et al., 2009) only a third of coronary patients attended cardiac rehabilitation, whereas two-thirds joined the EUROACTION programme. Recruitment was even better in primary care, with nine out of ten patients joining the programme. This might be explained in part by the use of motivational and cognitive invitation approaches that have been shown to be effective by randomised controlled trial evidence (Davies et al., 2010; Wyer 2001; Hillebrand 1995). The considerable uptake in the general practice part may be a consequence of a very client-centred and flexible approach, with individual appointments being made at the convenience of each participant, together with greater access as it was delivered at the family doctors surgery close to the patient‘s home.

A fourth strength is that the analysis was by ‗intention to treat' because all patients and partners identified at baseline, irrespective of participation, were invited back at 1 year. Not every eligible individual who consented to participate did so and other individuals did not participate fully, but they were all invited to the 1-year assessment regardless. In the hospital study, of the 126 patients who consented but then did not participate 40% attended the assessment at 1-year. Of the 166 patients who only partly participated in the programme, 37% returned at 1-year. Conversely, around 7% who did take part in the 16-week programme did not then attend the assessment at 1-year. In general practice, almost one in five patients who consented but did not then participate in the programme attended the assessment at 1-year. In addition, almost 1 in 10 patients who fully participated in the programme did not then attend the assessment at 1-year. Whilst it reduced selection bias by inviting all eligible patients to the 1-year assessment, the implication was that the treatment effect in the hospital study was likely to be an underestimate.

A fifth strength was that this was a multicentre trial. This does, however, present many challenges but does increase the generalisability of findings. Although EUROACTION and this sub-study within the trial study were both not sufficiently powered in the end to detect a treatment effect at a country level, due to less recruitment than expected and greater than anticipated heterogeneity, the results for physical activity and fitness generally demonstrated that the intervention had a significant impact in most countries. Moreover, the 12 pairs managed to recruit a comparable number of subjects overall. Consequently the analysis at 1-year comparing INT with UC was very balanced for sample size as a whole.

Sixth, with regards to the outcome measures employed by this study to assess physical activity participation and fitness there were a number of features that aimed to make the EPAF-Study robust. The multidimensional nature of physical activity makes assessing it extremely difficult. Given the associated health benefits of *physical activity participation* and *physical fitness*, measurements were carefully selected to capture both independently. For physical fitness, objective measurement using a sub-maximal exercise test was implemented, as opposed to estimating fitness with questionnaire based methods or using a surrogate measure, such as grip strength.

Whilst resources did not allow for maximal cardiopulmonary testing, which would have been the gold standard, the sub-maximal tests selected have been shown to have high reproducibility and validity and in a population with CVD (Pepera et al., 2010; Buckley et al., 2004; Fowler et al., 2005). The Yamax Digiwalker SW200 was selected as one of the most accurate and reliable electronic pedometers available (Bassett and John, 2010; Schneider et al., 2004; Crouter et al., 2003; Schneider et al., 2003). The use of an accelerometer, however, (which also measures intensity) would have been superior, but was unaffordable.

Finally, staff also underwent competency testing in administering these physical activity and fitness measures. This aimed to provide a high level of quality assurance. This included an intensive training programme coupled with a detailed health professional manual to standardise delivery of the study protocol as intended. There were also follow-up quality assurance visits to all the centres by the author in some instances and the senior research fellow on other occasions to ensure the protocol was being followed. Hence there were good processes in place to try to make sure this was a high quality study. However, given the challenges faced analysing the physical activity and fitness data, the methods used to provide quality assurance could be further improved.

7.2: Study limitations and sources of bias

Whilst there was strength in the study design, there were also numerous limitations and various possible biases. In relation to statistical power, a matched, paired cluster-randomised controlled trial has inherent limitations. The main trial was statistically underpowered for three reasons. First, the number of patients recruited was much smaller than expected. Second, although pairs of centres were matched, initial patient assessment revealed some unexpected differences in patient characteristics—i.e, some favoured usual care and some favoured intervention. Third, heterogeneity between pairs of centres for some results because of the small number of pairs also reduced the study‘s power.

In addition, there may have also been an overestimation of treatment. Not all those at baseline in the intervention groups came back at 1 year. These non-responders included a higher proportion of heavy smokers, obese, and sedentary patients than in the responders. However—the same bias is also true for usual care—of all those patients identified at baseline, slightly more than half came at 1 year.

This is concordant with other studies that suggest non-responders tend to have less healthy lifestyles and poorer risk factor control (Thomas et al., 2002; Garcia et al., 2005; Drivsholm et al., 2006; Boshuizen et al., 2006).

Whilst this non-participation can lead to selection bias, at least the same bias was introduced in both the INT and UC groups. On the other hand this loss of a selective group can reduce the external validity as well as the generalisability of the research findings. Although a quarter of eligible COR patients did not consent to take part, of those that did and came to the initial assessment 89% came back at 1-year. Retention was even better in the general practice study. Only 3% of HRI did not consent to take part in the study in INT and of those who attended the initial assessment 91% of them returned at 1-year. The success of any longitudinal study depends upon its participants remaining in the study. Whilst this possible selection bias is important to note attrition overall was extremely good. Consequently the degree of any overestimation of treatment effect was reduced.

Whilst the health profile of those few that dropped out of the intervention was poorer; women, the young and the very elderly were also less likely to consent to participate in the first instance. This is evidenced in the hospital study where 70% of the COR patients in INT and UC were male and the mean age was 63 years. With an ageing population and people living longer with conditions such as heart failure, there should be a trend for increasing age in cardiac rehabilitation settings. The limitation being that it is these more elderly individuals who currently do not access these services. For example, the latest NACR audit (2012) reports that despite overwhelming evidence for cardiac rehabilitation, only 1% of people with heart failure actually access a programme in England, Northern Ireland and Wales. It is therefore healthier individuals who routinely access these services. These are also people less likely to be depressed, socially isolated, unemployed or socially disadvantaged. People over the age of 65 years of age are more likely to suffer from loneliness, which is strongly associated with depression (Victor & Yang, 2012) and may also contribute to this reluctance to participate.

The EUROACTION population‘s sex and age distribution in the hospital study were on a par with those seen in the 40 RCT‘s evaluating exercise-based cardiac rehabilitation (Heran et al., 2011; Taylor et al., 2004) and the average for the UK (NACR, 2012). This makes these study findings generalisable to current cardiac rehabilitation practice in the UK. They reiterate however, that there are limitations in their generalisability to the elderly and to women.

Finally, in noting limitations that relate to the characteristics of the study population, despite the pairs of centres being matched before randomisation, there were some unexpected differences at baseline in the INT and UC populations who then consented to take part. Distribution for recruiting diagnosis for example differed significantly both in the hospital and general practice studies. In the COR population a greater proportion of patients with stable angina participated in INT, whereas UC recruited more patients‘ post myocardial infarction. The evidence for cardiac rehabilitation post MI is much stronger than that for people with stable angina; this being considered significant enough that the latest guidelines from the National Institute for Health and Care Excellence (NICE) do not recommend cardiac rehabilitation in this latter group (NICE, 2012).

This same guideline is however, contradictory and does recommend all the separate core components of cardiac rehabilitation (health behaviour change and education, medical and lifestyle risk factor management, psychosocial health and cardioprotective therapies) as well as recognised programmes, such as the Angina Plan, which are home-based models of cardiac rehabilitation. Since stable angina and post MI share the same risk factors it seems illogical to conclude that one group would benefit from a structured programme of care whilst the other would not. What this does highlight however, is that the RCT evidence for cardiac rehabilitation and similar prevention programmes in those with stable angina is lacking. This also suggests that the EUROACTION programme might be less effective in those with stable angina than in people post MI. Usual care could therefore be in an advantageous position, given there was a greater proportion of people post MI in this group.

Similarly, the same was seen in general practice but this time any bias would be in favour of the INT group. The INT group had a greater participation rate from those already on treatment for hypertension and / or hypercholesterolemia and people with known diabetes than people who had been identified through a HeartScore> 5%. The Cochrane review by Ebrahim and colleagues (2011) demonstrated that prevention programmes that share some of the EUROACTION approaches have a bigger impact on these individuals with labelled conditions and have very little effect in the general population.

In addition, it is not known if objective physical activity participation and cardiorespiratory fitness at baseline were matched in the COR patients as these were not measured in UC. In general practice it was measured and despite physical activity participation being similar, the UC group were on average fitter than their counterparts in INT (although not statistically significant). The analyses did not adjust for these differences at baseline and in this particular case it did not matter. The patients in UC did not improve any further, and if anything their fitness reduced a little over the course of the year, whereas in INT there were sizable gains. A significant difference in the change in fitness between the baseline and 1-year assessments was found, in favour of INT, and whilst this was a positive result, given the baseline differences, it may be an underestimate of the treatment effect.

The effect of this physical assessment activity in a random subsample of UC (UC-SS) could also lead to an underestimate of treatment effect. Around 20% of patients in UC had a comprehensive baseline assessment alerting them and their doctors to the need for change. Moreover, in the hospital UC-SS, they were also exposed to an additional assessment at 16 weeks. In terms of physical activity there were indications that these two assessments in UC preceding the final review at 1-year, had an impact on activity levels in coronary patients. The difference in the magnitude of difference in the proportion of patients achieving the EGPA at 1-year was considerably less in INT *vs* UC-SS versus INT *vs* UC overall. In general practice, there was no evidence within the physical activity and fitness results to indicate that exposure to assessment alone changed behaviour.

There are two further reasons for a possible underestimation of treatment effect. First, centres randomised to usual care knew they would be audited which might have led to improved practice and there is evidence to suggest that this was indeed the case. The EUROASPIRE III study spans 22 European countries in a survey of the management of coronary patients together with 8 European countries investigating the management of patients at high risk of CVD treated in general practice (Kotseva et al., 2009a; Kotseva et al., 2010). Six of the eight countries in EUROACTION participated in EUROASPIRE III allowing for some comparing of observed practice. As published in the main trial (Wood et al., 2008), the proportions of patients in UC achieving blood pressure and cholesterol targets were considerably higher in the EUROACTION study than those observed in the EUROASPIRE III surveys. This would suggest that ‗usual care' comparator in EUROACTION may not reflect the norm and there could be an underestimate of treatment effect.

Second, almost a fifth of usual-care patients received some form of structured cardiac rehabilitation that will have had some similarities to EUROACTION interventions. For example in both Sweden and the UK it was impossible to find a large enough pair of district general hospitals that did not provide a cardiac rehabilitation service. In the UK the UC centre had a nurse-led cardiac rehabilitation programme which included a full-time physiotherapist and some dedicated dietetic time. Patients actually attended this programme in UC twice a week and the content of the sessions was not dissimilar to that being provided in the INT. The expectation is that a structured cardiac rehabilitation programme like this would also achieve some improvement in health-related outcomes. Hence, this would account for an underestimation of the treatment effect overall.

Locality of centres should also be considered in the study limitations. This applies more to the hospital study where the centres were placed geographically far apart. Access to physical activity opportunities may have been entirely different with prom walking, beach activities and water-based sports, for example, being more readily accessible in UC compared to a busy city suburb. Physical environment is recognised as one of the determinants of cardiovascular disease and it should be noted that these geographical differences may have contributed to the heterogeneity in the study findings.

During the visits made to the centre differing infrastructure and levels of community engagement could be observed. For example, in Italy the INT hospital principle investigator was a well-known and reputable community leader. The EUROACTION INT programme lasted 16 weeks in total with a follow up at 1-year and the study did not include a set protocol for an intervention once this initial 4 month programme had ended. The Italian INT centre also organised a number of activities and reunions such as quarterly _fun runs‘ and family health days where they invited all past participants to join. Local restaurants also became involved in a _menu labelling‘ initiative where certain recipes were _kite marked‘ as _EUROACTION friendly‘. Whilst certainly to be admired this does raise questions as to how much the EUROACTION intervention itself achieved and how much of the sustaining of health behaviours were a consequence of initiatives such as these that were not specifically in the protocol. However, it illustrates very well how a prevention programme can influence community-health more widely.

A further source of bias is the lack of blinding. The centres were randomised to either carry on as normal or deliver the EUROACTION programme; which essentially became the _norm‘ for the INT centre. Patients were then approached by these centres with treatment allocation already known. Patients consented to allow their data to be used for research purposes. It was therefore not relevant for patients to know that their care was being evaluated specifically against another approach. Besides, it would be impossible to blind patients from preventive cardiology practice. However, it should be recognised that this lack of blinding does introduce a bias. Those patients exposed to a 16-week or 1-year intervention were well-informed regarding the physical activity targets for improved health and well-being. They also may not wish to disappoint their care-providers. Whilst this may be the standard for the National Health Service in the UK, this is not the case for Europe more widely. There is, consequently, a need to be sensitive to the fact that the patients, and more consistently those in the INT or UC-SS groups, may have over-reported their physical activity status to be perceived as _goodpatients‘.

Those collecting the physical activity and cardiorespiratory fitness outcome data were also not blinded to treatment allocation which introduces further potential bias. The pairs of centres were required to consent to take part in the study before randomisation. In personally meeting the national coordinators and principle investigators for each of the centres it was clear that all were hoping to be allocated the EUROACTION intervention. Given that the collective team were committed to raising the standards of preventive care, this lack of blinding could also introduce bias.

There is however, a converse argument. According to the protocol, nurses in usual care were to identify patients‘ problems and then signpost to solutions without offering advice. Nurses are however by profession caring and it would be unsurprising if they did not provide some advice and support during the consultation. This was evidenced in that one of the usual care centres the nurse had to be replaced. During the first quality assurance visit it had been identified that she was not just assessing and signposting to care but offering detailed personalised advice and essentially delivering the EUROACTION intervention. She developed a close friendship with the EUROACTION INT nurse who had shared the INT health professional manual with her. On reflection these were not research nurses and came from clinical backgrounds. This highlights the deeper complexities in carrying out a study of this nature.

There was also a degree of missing data for physical activity participation and cardiorespiratory fitness and some information that one could argue was dubious. As illustrated by Tables 5.1.1 ad 6.1.1 the self-reported physical activity was almost complete; noting this was the least objective of the measures though and limited by recall bias. On the whole, data was more complete in general practice than in the hospital study.

Each centre was supplied with a stock of pedometers at the start of the study and as identified the hospital study preceded that in usual care. The UC nurses were generally carrying out a one-off assessment which finished with the patient being supplied with a pedometer and a step diary together with an addressed envelope to return these. Pedometers and step data were not being returned and availability then became problematic. If consecutive patients received the pedometers whenever they were available this should not have introduced bias. However, if the nurses in UC had selected only the least active to receive the pedometers this would

result in an overestimation of treatment effect. If people who were more active returned their data more than the sedentary this would, conversely, underestimate the treatment effect.

A further limitation with regards to the objective physical activity participation measure was that it was collected the week following the self-reported data and therefore was not measuring exactly like for like. As already mentioned there are numerous limitations in the pedometer such as being insensitive to many activities and being unable to quantify intensity or energy expenditure. Ultimately the pedometer is a crude measurement device for physical activity participation and if finances had of allowed a triaxial accelerometer would have been preferable.

The difference in participation rates for the fitness tests is more difficult to explain. As highlighted previously in the hospital study physiotherapists carried out the test in INT and nurses in UC. It was hypothesised that the nurses were more selective and did not include frailer people or people with comorbidities. Conversely the physiotherapists, given their experience in dealing with comorbidities and exercise, were confident in including almost all the patients. Formal analysis did not support this hypothesis and the difference in participation remains unexplained.

In general practice, nurses carried out the fitness test in both INT and UC. Nevertheless, there was still a difference in participation rate between INT and UC (65% and 81% respectively). If there was any systematic selection occurring this would introduce bias. For the random subsample in INT however, the majority of fitness data was complete resulting in a more robust comparison.

On reflection, having physiotherapists in INT and nurses in UC in the hospital study proved problematic. For the main trial due to the nurses misclassifying physical activity status resulted in the 7-DAR dataset for the entire cohort having to be recoded using a blinded randomly ordered approach to ensure scientific validity. For administering the step count data collection the difference in professional backgrounds was unlikely to impact but for the cardiorespiratory fitness data the author hypothesises that the nurses and physiotherapists may have differed considerably in their confidence with this regard.

In summary, there were several strengths but also a number of limitations and sources of bias. Some of these biases lead to a likely overestimation of treatment effect whilst others an underestimation.

7.3: The effectiveness of the EUROACTION programme in raising physical activity participation and cardiorespiratory fitness at 1-year

Before interpreting these findings, a reminder of the subtle differences between the primary objectives in the hospital and general practice study are presented below in Figure 7.3.1.

Figure 7.3.1: Primary study objectives

HOSPITAL study objective:

To evaluate the impact *at 1-year* of a ***16-week physiotherapy-led physical activity and supervised exercise intervention*** on *objective physical activity participation* and *cardiorespiratory fitness* in ***coronary patients*** compared to usual care.

GENERAL PRACTICE study objective

To evaluate the impact *at 1-year* of a ***1-year nurse-led physical activity intervention*** on *objective physical activity participation* and *cardiorespiratory fitness* in ***high risk patients*** compared to usual care.

Whilst differences in mean steps per day *(objective physical activity participation)* and performance measures in the Incremental Shuttle Walk Test (ISWT) (hospital) or Chester Step Test (CST) (general practice) *(cardiorespiratory fitness)* were all in the same direction, in favour of the INT, the only result which achieved a statistically significant difference at the 5% level was the difference in mean steps per day in the hospital study (Table 7.3.1).

At face value this raises doubts as to the added value of the EUROACTON programme as an intervention to successfully increase physical activity levels. Whilst the results would suggest the hospital programme did increase physical activity participation, this did not translate to a statistically significant improvement in cardiorespiratory fitness. Given the evidence base presented earlier that highlight the immense health benefits associated with increases in aerobic capacity these results, at seeming worth, were disappointing overall (Chapter 2).

Table 7.3.1: Summary of results for the primary objectives

Physical activity participation at 1-year	**COR** **(INT versus UC)**	**HRI** **(INT versus UC)**
Subjective previously published reference: Proportion achieving self-reported physical activity target at 1-year	**Δ +35.6%** (+20% to +51.1%) P=0.002	**Δ +29.4%** (+10.5% to +48.2%) P=0.01
Objective comparator: Mean steps per day at 1 year	**Δ +2310 steps** (1226 to 3394) P=0.003	**Δ +982.0 steps** (-569.4 to +2533.4) P=0.17

Cardiorespiratory fitness at 1-year	**COR** **(INT versus UC)**	**HRI** **(INT versus UC)**
Mean performance distance or minutes achieved	**Δ +54 metres** (-102.8 to +211.0) P=0.42	**Δ +0.99 minutes** (-0.45 to +2.42) P=0.14

COR = coronary patients in hospital study HRI = high risk individuals in general practice study

7.3.1: Statistically significant versus clinically meaningful results

However, it is of paramount importance to avoid evaluating findings based on the p-value in isolation. Published data on the minimum clinically important difference in steps per day and distance achieved in the ISWT allude to the results representing a meaningful impact in physical activity participation and cardiorespiratory fitness. A large review by Tudor-Locke et al., (2004) report a difference in excess of 775 steps per day as a clinically meaningful difference in people with a clinical condition including: heart disease, stroke, claudication, diabetes and hypertension. Likewise, according to Singh et al., (2008) a minimum clinically important improvement for the ISWT is 47.5 metres. Although for this latter finding it should be noted that this was in a pulmonary rehabilitation population and may not therefore be representative.

Evidence would suggest the EUROACTION programme achieved clinically meaningful differences in both physical activity participation and cardiorespiratory fitness. The original sample size calculations for this study (Figure 3.9.1) would suggest this study was sufficiently powered for analyses of steps per day and cardiorespiratory fitness at a European level (and not for a within country analysis). In fact, this study became considerably underpowered due to the larger than expected degree of heterogeneity observed.

7.3.2: Loss of statistical power

To explain this important point, using the actual baseline data for the ISWT (mean 350 metres and a standard deviation of 170 metres) the sample size calculations were repeated (Table 7.3.2).

Table 7.3.2: Sample size calculations for the ISWT using the EUROACTION study population

Change	Difference in metres	Sample size required
5%	17.5	1482 per group
10%	35	371 per group
15%	52.5	165 per group
20%	70	93 per group

Based on a 15% increase representing a clinically important difference this would be a difference of 52.5 metres (Table 7.3.2). This study observed an actual difference of 54 metres, and yet this was not nearly statistically significant. This was because the study used a standard sample size calculation that assumed all values are independent of each other. In reality, there was strong clustering observed within countries which had a major impact on the volume of available data.

The addition of a value to account for the size of the clustering and inflate the sample size accordingly, known as an intra-class correlation, would have been preferential. Essentially, due to the large degree of heterogeneity observed between countries and within countries (illustrated throughout the results), this study was considerably underpowered to show such a difference in both steps per day and cardiorespiratory fitness as being statistically significant.

Given the above, the results for to the primary study objectives should be interpreted with these considerations in mind. Essentially, there is strong evidence to support the 16-week physiotherapy-led EUROACTION physical activity intervention was effective in increasing physical activity participation, which was supported by inferential analyses ($P<0.05$). This translated to a clinically meaningful increase in cardiorespiratory fitness which was underpowered to detect a statistically significant difference. The physical activity intervention in general practice also achieved clinically meaningful improvements in objective measures for physical activity participation but the magnitude of the effect size was weaker and not statistically significant.

7.3.3: Sustaining increases in physical activity behaviour

An important new finding is that the difference in physical activity participation was at 1 year. This was 8 months after participants had completed the physical activity and exercise intervention in the hospital study. Long-term adherence to a healthy lifestyle remains one of the most difficult problems in secondary prevention of CVD. Prevention and rehabilitation programmes typically rely on short-term exposure to lifestyle behavioural interventions and risk-factor modification to gain long-term benefits in terms of quality of life and reduced morbidity and mortality. Risk factors and lifestyle behaviours have generally been demonstrated to deteriorate after completion of a cardiac rehabilitation programme, indicating that the intervention in the long term may be inadequate (Kotseva et al., 2009; Scrutinio et al., 2009; Le Masurier& Tudor-Locke, 2003).

A further important discovery is that this study highlights that the EUROACTION programme may not be as effective at increasing physical activity participation as first presented in the trial‘s publication of its results (Wood et al., 2008). The main findings support the tendency for over-reporting physical activity when assessed using methodologies based on recall (Sallis and Saelens, 2000; Shepherd, 2003).The subjective self-reported outcome for physical activity participation indicated the potential for an artificially inflated effect size when compared to more objective findings. However, it is also important to bear in mind that the pedometer used was insensitive to activities that took place with the upper-body or activities such as swimming and cycling and was only equipped to register approximately 90 per cent of activity (Schneider et al., 2003; Ward et al., 2005).

7.3.4: Evidence of selectivity and that intervention intensity matters

Essential to note was evidence of possible selectivity. Only 52% and 62% of the coronary patients in usual care had step count data and fitness outcomes for the ISWT respectively (Table 5.1.1). For step counter data in the hospital study there were known reasons for this. At one point in the study the pedometer stock in usual care became critically low. This was a result of some participants not posting back the pedometer or log sheet. Loss in this way was not anticipated and was not an issue in the intervention group as they had far more direct contact with each participant. Consequently there was a period where it was not possible to collect step data on every consecutive patient in the hospital UC group.

A selection bias was possible but was not substantiated by a statistical comparison between those with and without data based on age, sex and the self-reported results for the achievement of the European guidelines for physical activity (EGPA). Very little step data was missing in the general practice study which followed, as better systems were put into place to ensure the return of pedometers and log books.

Whilst there was more complete data for step counts in the general practice study, unlike in the hospital study, this more objective outcome did not support the differences in self-reported activity at 1–year to the same magnitude. At 1–year HRI in INT were achieving on average 7722.5 steps per day compared to 6675.2 steps per day in UC; an absolute difference of +982.0 (95% CI, -569.4 to +2533.4; P=0.17). It is possible that the smaller treatment effect size may be a consequence of the intensity of the intervention. In the general practice study, nurses in INT provided a comprehensive assessment of physical activity coupled with tailored advice and signposting to appropriate exercise-related services and facilities available in the local community. Unlike the hospital study, there was no 16-week supervised exercise component and there was no access to a specialist physiotherapist.

7.3.5: Heterogeneity and its impact on statistical power

There are a number of complexities which must also be considered when interpreting these results. As the results show, in absolute terms the mean steps per day for INT in hospitals and general practices were similar as were the mean steps in UC hospitals and general practices. Yet, the difference in mean steps per day, INT versus UC, was statistically significant in the hospital study but not for general practice. This is because in the former all INT centres moved in the same direction (Figure 5.2.1). This was not the case in the general practice study where there was more variation (Figure 6.2.3). Even though 4 out of 6 countries were clearly in favour of INT with the one remaining centre equivocal, Poland moving in the wrong direction and to this magnitude was enough to completely lose statistical power to detect a statistically significant difference.

7.3.6: Possible reasons for the discrepancies in step data

The reasons why Poland was so different are not fully understood. Both the INT and UC general practices were geographically close and shared the same local infrastructure so an ecological or geographical difference to account for this result is unlikely. The data was also almost complete and therefore any systematic selection is also unlikely. One possible explanation is that perhaps the standardised instructions were not followed in the UC practice. These instructions were specifically to behave as ‗normal' as it is recognised that wearing a motion device motivates physical activity behaviour (Tudor-Locke, 2002). In addition, if the nurse in UC (or even a poster in the general practice centre) gave information regarding the public health goal of 10,000 steps per day this could very well motivate participants to try to achieve this during the week of measurement.

With regards to achievement of this public health goal, pedometer data revealed a difference of 2,310 steps per day in favour of the INT at 1-year in the hospital study. This equates to just over one additional mile of walking per day. This is an encouraging result but the mean steps per day observed fell considerably short of the national guideline of 10,000 steps per day and a very small proportion of COR and HRI actually achieved this. The 10,000 or more steps per day recommendations are based on young middle aged subjects with normal anthropometric measures and may not apply to this older and obese population where steps counts are typically underestimated (Tudor-Locke & Bassett, 2004). The EUROACTION findings suggest it is not appropriate to recommend this generic target in these population groups.

A further consideration when interpreting the results in relation to the primary study objectives was a possible systematic error in measurement. All the patients in the INT group had previous exposure to the use of a pedometer before the assessment at 1-year. In the UC group 80% of patients were using the pedometer for the first time at 1-year. Given the motivational effects associated with wearing a pedometer for the first time it is possible the results represent an underestimate of the true treatment effect for means steps per day (Tudor-Locket, 2002).

7.3.7: Interpreting the outcomes for cardiorespiratory fitness

Moving on to the results for cardiorespiratory fitness, the difference in participation rates between INT and UC for the ISWT (Table 5.1.1) and the CST (Table 6.1.1) was complex. For the former, the results allude to enormous differences in ISWT participation between centres within countries and between countries (Table 5.3.1). The largest discrepancy was observed in Spain where 96% of INT patients completed an ISWT compared to just 37% in UC. It is unlikely that 63% of usual care patients were not clinically stable enough to participate in the test. Had more usual care patients participated, it is possible that the estimated treatment effect in Spain would be quite different. Appendix 9 highlights the UC centre in Spain ranked lowest for both the proportion of COR patients achieving the EGPA as well as mean steps per day at 1 year. It is possible then that in UC Spain only the fittest patients were included in the ISWT, which could explain why the mean number of metres scored for this centre was much higher than expected.

There were other anomalies. The UC centre in Italy had unusually low scores in the average metres achieved in the ISWT (Appendix 9). Similarly, given the high participation rate in the ISWT in the INT centre in Spain (96%), the mean metres scored are much lower than other INT centres with a similar uptake, such as Sweden and the UK. Comparisons of characteristics of those with and without ISWT data did not substantiate a selection bias.

For the general practice study it was the reverse and the participation rate in INT was considerably lower than that in UC. Once again those with missing data were comparable to those with data for age, sex and achievement of the EGPA. The CST results provide no evidence of a statistically significant difference overall in the minutes achieved between groups (Table 6.3.1). It should be noted however that four out of six countries demonstrated a significant difference, in favour of INT (Denmark, Italy, Netherlands and UK). The opposite was found in one cluster (Spain) which contributed significantly to the loss of statistical power (Figure 6.3.1). This is another example highlighting the major impact of heterogeneity in power to detect a statistically significant difference.

All of these discrepancies (in the hospital and general practice study) make it very difficult to draw strong conclusions as to the effectiveness of the EUROACTION programme at increasing cardiorespiratory fitness compared to usual care at 1-year. Overall, it can be concluded that the primary results for this study provide some good evidence that the EUROACTION programme better increased physical activity participation and cardiorespiratory fitness than usual care. Whilst not every result was statistically significant the absolute differences achieved (in an underpowered study) represent clinically meaningful changes. The EUROACTION model has shown its efficacy above current practice in achieving increased physical activity participation. These findings add new knowledge on interventions that are effective for people at risk of developing cardiovascular disease and people with established coronary heart disease.

7.3.8: The added value of a physiotherapy led intervention

The overall findings also indicate that the EUROACTION physiotherapy-led 16-week intervention, that included a supervised exercise component and the support of a multidisciplinary team, had a greater impact than a practice nurse delivering a physical activity intervention based on motivational interviewing over the course of a year. This directs to the added value in adopting of a more intensive approach and the benefits of incorporating physiotherapists as an integral part of preventive cardiology programmes more widely. This recommendation however recognises the two interventions were not delivered to the exact same populations. Consequently, a future research recommendation would be to evaluate the impact of this physiotherapy-led physical activity intervention in community settings, such as general practice, in high risk individuals.

7.4: Changes over time in physical activity participation and cardiorespiratory fitness

The secondary objective of the EPAF-Study was to evaluate the impact of the programme in physical activity participation and cardiorespiratory fitness in a comparison of change over time. In the hospital study, the usual care group did not participate in an objective physical activity assessment at baseline, which on reflection was a considerable limitation given the high degree of heterogeneity experienced between and within countries. Any differences in physical activity behaviour and fitness at baseline were essentially unknown and therefore the primary analyses at 1-year of INT versus UC could not be adjusted accordingly.

Given this study used randomisation by centre (cluster) as opposed to individual randomisation it is entirely possible there were differences in physical activity participation and cardiorespiratory fitness between INT and UC at baseline; especially given there were significant differences observed with regards to baseline characteristics such as recruiting diagnosis.

The primary analyses presented in the previous section include 1-year data and take no account of differences between the populations at baseline or any systematic errors that may have occurred within any of the centres. In the general practice study, all three physical activity and fitness measures were included in the assessment at baseline and 1-year in both the INT and UC groups. This allows for a much more robust analysis. Any differences in the population characteristics, geographical location or methodology applied in each centre were essentially nullified as this was paired data. Change between these two time points was measured under the same conditions in each centre. Consequently this analysis of ‗change over time' within a centre and then ‗difference in change' between centres within a country and between countries was better placed to detect the true differences observed between INT and UC.

7.4.1 : Changes over time in physical activity participation and fitness in coronary patients

The results show that the EUROACTION physical activity and exercise intervention in the hospital INT group significantly increased physical activity participation (both subjectively and objectively measured) and cardiorespiratory fitness over time ($P<0.0001$ in all). The magnitude of change also clearly exceeds the minimum clinically important difference across all parameters (Appendix 9). This result in isolation strongly supports investment in the EUROACTION model as an effective measure in reducing the implementation gap in translating prevention guidelines to clinical practice reported earlier.

A further important finding is that this EUROACTION model of cardiac rehabilitation used a once weekly supervised exercise methodology as opposed to the twice or even three times per week approach recommended by national guidelines and randomised controlled trials (SIGN, 2002; Taylor et al., 2004). At baseline, COR patients in INT scored on average 324 metres in the ISWT; this being level 6 in the test. Using MET values derived from people post MI performing the ISWT (Woolf-May & Ferrett, 2008), the walking speed for this level translates to 6.6 METs. Since the test was stopped at 85% of HRmax it can be predicted that the average METmax for the EUROACTION patients in the hospital study at baseline was

approximately 8.5 METs. At 1-year, COR patients in INT scored 415.5 metres, which is level 7 and equates to 7.3 METs and a predicted METmax of 9.5 METs (BACPR, 2012).

In referring to the large body of observational data presented in Chapter 2, fitness is a strong predictor of all-cause mortality. Men and women with an exercise capacity (or METmax) of more than 10 and 9 METs respectively have the greatest protection (Myers et al., 2002; Kavanagh et al., 2002; Kavanagh et al., 2003; Franklin et al., 2004; Kokkinos et al., 2008; Kodama et al., 2009). In addition for every MET gained there is an 8-17% reduction in mortality (Blair et al., 1995; Dorn et al., 1999; Myers et al., 2002; Gulati et al., 2003). These results therefore highlight that the EUROACTION intervention results for changes in fitness are clinically meaningful.

These gains of 1 MET are also meaningful in the context of recent findings by Sandercock et al., (2013). They highlight that typical cardiac rehabilitation programmes in the UK are achieving gains of on average 0.52 METs, which is only a third the mean estimate reported in the most recent systematic review of cardiac rehabilitation (1.55 METs) (Heran et al., 2011). Hence, it would appear that the EUROACTION model achieves greater fitness gains than currently typical for the UK but that the intensity of the intervention remains suboptimal. Programmes included in the Cochrane review lasted 3.8 months on average with supervised exercise sessions 2-3 times per week. In contrast, the EUROACTION intervention lasted 3 months and included once weekly supervised exercise, but with a strong emphasis on home exercise, which could explain this shortfall. Future research testing the EUROACTION model delivered using a twice weekly approach would be of benefit.

The EPAF-Study findings suggest this model of cardiac rehabilitation better increased cardiorespiratory fitness than typically observed in the UK. This also concurs with a large trial‘s findings in Italy. The Global Secondary Prevention Strategies to Limit Event Recurrence After MI (GOSPEL) trial (Giannuzzi et al., 2008; Giannuzzi et al., 2005) similarly demonstrated the impact of a multidisciplinary programme on lifestyle behaviours, risk factors management and use of cardioprotective drug therapies in patients with CHD. This was an RCT across 78 cardiac rehabilitation centres in Italy which included follow-up and found these changes translated to a significant reduction in cardiac events. At 6 months, the difference in the level of physical activity from baseline between the two groups was higher in the intervention group and it was maintained throughout the study (23.8 vs 18.8%; p=0.01).

In the EUROACTION trial *within Italy* at 1-year 42.8% of INT patients were achieving the European guidelines for physical activity participation versus 23.0% in UC (+19.8%; 95% CI 10.3% to 29.3%) (Wood et al., 2008). This is another important finding as it highlights that physical activity levels observed in the Italian UC group were representative. The results achieved in EUROACTION both within Italy and at a European level were far better for physical activity participation (53.8 vs 19.6%; p=0.002) than those in the GOSPEL trial and consequently provide new knowledge in raising the benchmark for the standards of preventive care.

Accordingly it is concluded from the EPAF-Study that the EUROACTION programme was effective in increasing physical activity participation and cardiorespiratory fitness in people with coronary heart disease. Further, this model of care provides unique and important findings that should be recommended and used in routine clinical practice.

7.4.2 : Changes over time in physical activity participation and fitness in high risk individuals

The EUROACTION INT in general practice significantly increased subjective and objectively measured physical activity participation. The magnitude of change in both instances was also clinically meaningful (Appendix 9). This translated to a trend for increased cardiorespiratory fitness that was of borderline significance (P=0.06).

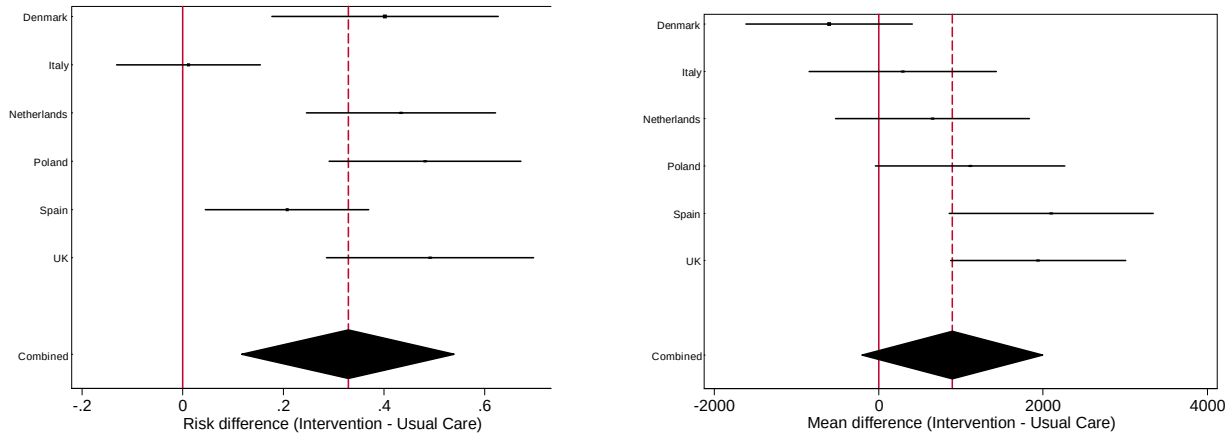
These changes in physical activity participation translate to considerable improvements in health outcomes. Achieving the guidelines for physical activity participation is associated with: a 25-46% reduction in risk of type 2 diabetes (Knowler et al., 2002; Hu et al., 1999;Knowler et al., 2002; Hu et al., 1999); a 30% reduction in cardiovascular events (Manson et al., 2002); a 30-40% lower rate of MI (Knowler et al., 2002; Hu et al., 1999); and a 50% reduction in CHD risk (Manson et al., 2002). Hence these findings contribute new knowledge to the evidence base in the prevention of cardiovascular disease prevention and highlight opportunities for general practice to better implement prevention guidelines and contribute more to reducing the burden of cardiovascular disease than is currently being achieved in routine clinical practice.

The change over 1 year in UC in self-reported activity followed the *exact* same direction as those seen for fitness (Appendix 9). These reductions observed are a major concern and highlight a widening gap in the implementation of CVD prevention guidelines within these general practices. The difference *in the difference* in change over 1-year between INT and UC was also statistically significant in both cases. This new knowledge provides further evidence to support that is possible to raise the standards of preventive care through the implementation of a preventive cardiology programme in general practice.

So why did the mean steps per day not follow suit and decrease over the year in the UC group? Given that this analysis of change over time used paired data which overcomes the issue of heterogeneity to a large degree this conflicting finding was unlikely to be due to the between and within country differences encountered in the primary analyses at 1-year. One important consideration (that was noted earlier), is that wearing a pedometer influences physical activity participation in itself. Pedometers are measurement tools but also motivational devices and increase walking participation (Gardner & Campagna, 2011; Staudter et al., 2011). The pedometer was worn the following week to the measurement of self-reported physical activity and this could explain the discrepancy.

Even though the mean steps per day over the year increased slightly in UC (+136 steps per day), this change was neither statistically significant nor clinically meaningful. The Forest plots for the change over time analyses concur with previous findings that self-reported activity was inflated compared to the more objectively measured steps per day (Figure 7.4.1).

Figure 7.4.1: Comparison of forest plots for difference in change in EGPA and mean steps per day over 1 year in the general practice study



a. EGPA

b. Steps per day

In translating the gains in cardiorespiratory fitness, it took on average 6.60 minutes and 6.81 minutes to achieve 80% of HRmax at baseline in INT and UC respectively. This was less than a minute into Level 3 of the test with completion of Level 2 and the achievement of 5 METs (BACPR, 2012). Extrapolating from this submaximal data an aerobic capacity (METmax) of approximately 7.1 METs was estimated. At 1-year, in INT the test time to an end point of 80% HRmax lasted on average 7.20 minutes which was approaching the end of Level 4. This represents a score of 6 METs and an estimated METmax of 8.6 METs (BACPR, 2012). In UC, the time to test completion reduced to 6.31 minutes. Whilst this was an absolute reduction, these patients in UC were performing at the same MET values and exercise capacity as seen at baseline.

Gains of at least 0.5 METs are clinically meaningful and have consistently been shown to be associated with lowered all-cause mortality and improved health outcomes (Blair et al., 1995; Dorn et al., 1999; Myers et al., 2002; Gulati et al., 2003). The EUROACTION intervention in general practice achieved an increase of 1.5 METs which translates to a 12-26% reduction in all cause mortality.

These findings challenge the latest Cochrane review on multiple risk factor intervention for primary prevention of coronary heart disease (Ebrahim et al., 2011). This review included 55 randomised trials that evaluated education and counselling interventions that aimed to reduce more than one risk factor (multiple risk factor intervention) in people without evidence of cardiovascular disease. The trials lasted between six months and 12 years duration and were conducted in several countries over the course of four decades. The median duration of follow up was 12 months (with a range of six months to 12 years). This review found that these interventions achieved only small changes in risk factors. Contrary to expectations, multiple risk factor interventions had little or no impact on the risk of coronary heart disease mortality or morbidity. The authors concluded that interventions using counselling and education aimed at behaviour change in the general population are limited and do not appear to be effective. The EUROACTION results, conversely, have shown that a family-based, nurse-led, multifactorial intervention delivered in a community setting that employs cognitive and motivational approaches to support behaviour change was associated with significant improvements in lifestyle and risk factor management (including physical activity).

Accordingly it is concluded by this EPAF-Study that the EUROACTION programme in general practice better achieved increases in physical activity participation and cardiorespiratory fitness in people at high risk of developing cardiovascular disease than current contemporary practice. This model of care should be recommended and used in routine clinical practice.

7.5: Other important findings to inform preventive cardiology practice

In evaluating the impact of the EUROACTION programme more completely it is important to discuss the generalisability of this study‘s findings. This study also purposefully employed evidence-based strategies to increase programme uptake, participation and completion and these findings have yet to be discussed and are included below.

7.5.1: The generalisability of study findings

The EUROACTION study population was highly representative with regards to physical activity status. As identified in the literature review the latest European statistics show that six out of eight countries included in the EUROACTION trial present with startlingly low but none the less above average participation rates for physical activity (Table 2.1.3). The ranking of the proportion achieving the European guidelines for physical activity (EGPA) almost mirrored EU rankings looking at the top and lowest four (Appendix 9). Given the EUROACTION study ran in just 12 hospital centres and 12 general practice centres this finding is important. It highlights that in each country the geographical locality was representative for the country as a whole and this study‘s findings are therefore generalisable.

Despite success in recruitment overall there were some differences in the characteristics of the study population with regards to age, sex and diagnosis. These need to be considered in the context of the results. Both sex and age were matched between hospital INT and UC centres. Mean age was similar and a greater proportion of the coronary patients were over the age of 65 compared to the study population in the general practice group with the mean age of the coronary patients being 63 years. This aligns with the mean age of participants in the RCT‘s for exercise-based cardiac rehabilitation presented in Chapter 2 (Heran et al., 2012; Taylor et al., 2004). But, this was also a criticism in that these studies included white middle aged men. It would appear that the EUROACTION study in coronary patients also recruited men (70%) who were generally less than 65 years of age. Consequently, findings from the hospital study have limited generalisability to women and the elderly.

Age and sex were balanced but recruiting diagnosis differed between hospital INT and UC centres. The hospital INT arm recruited a greater proportion of patients with stable angina than UC (36% versus 25% respectively), whereas the latter recruited more patients‘ post myocardial infarction or with unstable angina ($p<0.0001$). As the management of these individuals in relation to physical activity does not differ, this difference was not a major concern.

The general practice, whilst there was a statistically significant difference in age between INT and UC this difference equated to less than a year; 62 years and 62.8 years respectively. This is unlikely to be clinically meaningful as management is unlikely to be different due to this age difference of a few months. Males and females were evenly distributed throughout making this part of the study‘s findings more generalisable to men and women. There were however significant differences in recruiting diagnoses between INT and UC general practices. More individuals were recruited in UC into the HeartScore group (51% UC versus 42% INT) whereas INT recruited more patients already on treatment for blood pressure or cholesterol and patients with known diabetes ($p=0.0006$). This is important to note as RCT evidence would suggest primary prevention programmes are more effective in people with diabetes and people taking medications to modify cardiovascular risk factors than in apparently health people found to be at risk i.e. people without a ―labelled‖ condition (Ebrahim et al., 2011). This concurs with this study‘s findings too where the physical activity intervention was notably more effective in those with diabetes and hypertension or hypercholesterolemia. This difference results in a bias in favour of the EUROACTION programme in the general practice study.

Given the intensity of the intervention and the substantial time commitment involved from participants these attrition rates are striking and exceed European averages (70%) (Kotseva et al., 2009). The characteristics of those that did not fully participate are important to consider as this could introduce a further selection bias. The people who dropped out were more likely to be older and to be women. In hospitals; those with a diagnosis of stable angina and, in the general practice; those recruited through screening using HeartScore also dropped out more often.

For age and sex these findings are consistent with previous studies. There is a wealth of quantitative and qualitative data suggesting young patients in their forties and very elderly patients are less likely to participate in a prevention programme (Cupples et al., 2010; Beswick et al., 2005; Rees et al., 2005; Beswick et al., 2004; McCorry et al., 2009; Jones et al., 2007;Tolmie et al., 2009). The age categories used in the EUROACTION study were somewhat restricted but the dataset could be further explored to investigate the recruitment and completion patterns of the very young and elderly patients. In relation to sex, the EUROACTION findings support others in that women were less likely to participate and more likely to drop out (McCorry et al., 2009; Pullen et al., 2009).

Other population groups that are susceptible to drop out include: _well' patients, people with stable angina, people in general practice with a high risk score and those without as specific diagnosis, e.g. _hypertension' or _diabetes'. Being able to identify predictors of drop out is important and can facilitate better treatment in clinical practice. Future research on adherence could be of value in the design of subsequent interventions.

7.5.2: The impact of employing motivational approaches and early programme initiation

In noting that the EUROACTION physical activity intervention incorporated motivational invitation letters and telephone contact together with an early programme orientation approach it is important to evaluate their impact on uptake, attendance ad programme completion.

A quarter of the coronary patients in INT refused to take part (Section 6.1). In general practice only 3% did not agree to participate in the INT group. One could reasonably assume (in this case wrongly) that people following an acute event such as a myocardial infarction (MI) or following revascularisation procedures, such as coronary artery bypass (CABG) or angioplasty (PCI), would be more willing to take part in a preventive cardiology programme than the apparently well population within the general practice group. A greater time commitment from participants was required for the hospital study which is one possible explanation, and that these patients were _less well' at the time of being invited, could have influenced their willingness to participate.

There was also some drop out which was more prevalent in the hospital group. Of the coronary patients who consented most (89%) attended the initial assessment. Programme attrition was also reasonable; only 18% of these patients did not fully participate in the hospital intervention programme. In general practice, nearly every patient who consented to participate in the intervention attended the initial assessment (97%). However subsequent full participation in the intervention programme was similar in the hospital and general practice groups; 82% and 85% respectively.

Whilst an overall uptake of 67% to a preventive cardiology programme for coronary patients may seem low this is considerably better than the current national UK average (44%), as well as that seen across Europe (32%) as a whole (Kotseva et al., 2009). Percentages of patients who had an MI, a PCI, or a CABG taking part in cardiac rehabilitation in England, Northern Ireland and Wales are reported in the National Audit for Cardiac Rehabilitation (NACR) annual report. There has been a slow rate of improvement in the uptake of cardiac rehabilitation programmes with an increase from 38% (2007-2008) to 44% in the latest report (NACR, 2012).

This absolute difference of 23% in uptake to the EUROACTION programme has significant implications. Kaiser‘s and colleagues (2013) recently published cost model reported a £30 million saving being associated with increasing the national uptake for cardiac rehabilitation to 65%. However, it should be noted that this average is at a European level and there was much heterogeneity between countries. The uptake in the UK intervention centre was very good with 82% of all eligible patients attending the initial assessment and 74% returning to the assessment at 1-year. Given the many determinants of programme uptake, it should also be noted that whilst this uptake is very good it is based on one single centre in a fairly affluent location in England serving a predominantly white population. There are also many other examples of programmes in the UK with poor recruitment rates. It would be valuable to more closely evaluate the characteristics of exemplar programmes in terms of their design, approaches and level and type of professional support.

The greater reluctance in coronary patients to participate compared to apparently well people does not seem logical. Preconceptions that younger apparently well individuals would be less willing or committed to a 1 year preventive cardiology programme were incorrect. This does highlight the enormous opportunities for primary prevention as the vast majority of these asymptomatic individuals were willing to take part, joined and completed the programme.

Greater uptake and completion may be as the result of the approaches used as described in the methodology. As described previously, invitation was by letter and telephone contact and these specifically employed motivational approaches; a further feature shown in two RCTs to increase uptake (Wyer et al., 2001; Hillebrand et al., 1995). In the hospital study, coronary patients assigned to the INT started the EUROACTION programme within 10 days. This means that in the most part participants started the programme with little delay; unlike what is typical for the UK with an average waiting time of 56 days (NACR, 2012). Recent good quality RCT data supports this ‗early' approach. Pack et al., (2013b) conducted a single-blind, controlled trial comparing 10 days versus 35 days to programme initiation and found a significant improvement in attendance rates (77% versus 44%; $P<0.001$).

Finally, in addition to the above, the programme included a number of interventions to increase adherence. Planning and goal setting with regular review were of fundamental importance together with the use of diaries and a signed commitment from each of the participants. Again these are all principles that have been tested in randomised controlled trials; albeit of low quality (Sniehotta et al., 2006; Duncan &Pozehl, 2002). These specific interventions employed to increase patient uptake to the EUROACTION intervention and programme adherence were successful, although which of these components contributed the most remains unknown. These combined approaches worked in a European setting and should be recommended as standard. These new findings provide evidence that incorporating these innovations in routine clinical practice can effectively increase programme uptake and to levels that have been modelled to also be cost saving.

EUROACTION presents new and unique findings by demonstrating that it is possible to successfully engage the majority of patients with coronary disease and those at high risk of developing CVD in a preventive cardiology programme in settings generalisable to everyday clinical practice.

7.5.3: The need to look beyond preventive cardiology programmes

As promising as the results of this study appear to be, a high level of inactivity remained despite an intensive risk factor modification programme that has recently been costed in its application in the UK in the range of £1700 per patient (Matrix, 2014). Whilst the EUROACTION physical activity intervention more than doubled the proportion of coronary patients and people at high risk of developing cardiovascular disease, about half of these patients were still not sufficiently active (Figure 7.5.1). This subjective measure was further substantiated by a very low proportion of patients achieving more than 10,000 step counts per day.

Figure 7.5.1: Physical activity participation rates at 1-year

	COR INT	**COR** UC	**HRI** INT	**HRI** UC
% Achieving EGPA at 1-year	54	20	50	22
% Achieving $\geq$ 10,000 steps per day	28	9	26	19

COR = coronary patients in hospital study HRI = high risk individuals in general practice study

INT = intervention group UC = usual care group

Whilst clearly the EUROACTION programme was effective and should be applied to clinical practice more widely the results highlight that this model of care is far from offering the complete solution. With a large proportion of the study population remaining inactive this calls for greater investment population-wide measures. The exposure to risk factors is largely determined by an individual‘s circumstances and environment. To a large extent, factors such as location, genetics, income, education level and relationships with friends and family all have considerable impacts on health, whereas the more commonly considered factors such as access and use of health services often have less of an impact (WHO, 2011).

There is a great deal of interest in approaches to the prevention and management of cardiovascular disease that target people who are at high risk. However, despite positive outcomes from research (and substantiated by this study‘s findings), targeting individuals at high risk is at best likely to have a moderate impact (McQueen, 2013). The real challenge is to tackle the underlying determinants.

In the context of physical activity, this could be achieved by, for example, modifying environments to make them more conducive to physical activity. Create an attractive garden or playground and people are more likely to engage in physical activity. Other local population approaches can take the form of city councils building cycle paths which can encourage more people to use bicycles or to adopt a ciclovia approach where town councils can temporarily close streets for motorised transport to allow exclusive access to individuals for recreational activities and physical activity.

As presented in the introduction to this thesis, the need to address the global burden of CVD was evidenced by the ―High-Level Meeting of the United Nations‖ on Non-Communicable Disease Prevention and Control in September 2011, in New York. This was the second time only that the group had ever been called upon in relation to a health issue; the first meeting was in relation to Human Immunodeficiency Virus. This in itself speaks volumes. The United Nations and World Health Organisation (WHO) have committed to reducing mortality from non-communicable diseases by a quarter between 2015 to 2025 (the 25 by 25 declaration) (Horton, 2013). The findings of the EPAF-Study certainly contribute to this global agenda. However, they also allude to the fact that there is also an urgent need to look wider to population-based approaches to increase physical activity participation in combination with high-risk strategies such as the EUROACTION programme.

7.6: Future research recommendations

After all the possible caveats above are taken into account, this study has demonstrated that a structured physical activity intervention can successfully raise activity participation levels and cardiorespiratory fitness in Europe. The study has shown it is possible to raise the standards of preventive care currently being delivered and reduce the gap in the implementation of physical activity guidelines. Whilst clinically effective, further research is required to also evaluate whether this model of care is cost-effective. In relation to cost-analyses it would be useful to apply a similar model to that produced by Kaiser et al., (2013) to the EUROACTION programme and formally quantify the potential cost savings. Their recently published model demonstrates a saving of £30 million being associated with a 20% increase in uptake to cardiac rehabilitation across UK.

This study evaluated outcomes at 1-year and translated these changes observed to quantify health outcomes such as reduced mortality and morbidity by extrapolating findings from the existing evidence-base. Given additional funding, it would be worthwhile to follow-up the entire study population and properly monitor future events. Whilst the EUROACTION physical activity and fitness results are promising the longer-term impact has not been evaluated and this approach would benefit from being tested empirically, particularly with follow-up data for total or CHD mortality or clinical events, before being more widely promoted, particularly in developing countries where cardiovascular disease rates are rising.

The EUROACTION programme and physical activity intervention was not as successful in the recruitment of women compared to men. Similarly older people were less likely to participate. Whilst these findings concur with many other sources, gaining a better understanding of the reasons may contribute to the development of better strategies to target individuals with such characteristics. Whilst there is much supporting literature in relation to predictors of drop-out there is little good evidence on effective interventions that increase uptake and adherence within these population groups and future research in these areas is recommended.

In this study people with stable angina in the hospital population and those in the HeartScore group in general practices were more likely to drop out of the programme. This has not been reported elsewhere in the literature and consequently exploring the characteristics, barriers, health beliefs and motivators in these population groups more specifically would be of interest.

With regards to the management of stable angina the results of the present study would indicate that the EUROACTION programme was clinically effective. Currently, as highlighted earlier, NICE do not recommend cardiac rehabilitation to those with stable angina (NICE, 2012). This is most likely a consequence of the lack of high quality RCT‘s in this area. Given the wealth of evidence for the benefits of cardiac rehabilitation post MI, a condition that shares exactly the same risk factors, including people with stable angina could result in significant reductions in cardiovascular mortality and events. EUROACTION provides evidence supporting the inclusion of people with stable angina in a structured preventive cardiology programme, suggesting a high quality RCT is warranted in this population group specifically.

Given the enormous challenges faced when evaluating data and experiencing the impact of heterogeneity on statistical power the author would recommend any future cluster randomised controlled trials anticipate these challenges and utilise the EUROACTION data for sample size calculations with the addition of an intra-class correlation to account for the size of the clustering and inflate the sample size accordingly. This study has also demonstrated the advantages and recommendation to apply individual randomisation wherever possible as opposed to cluster-randomisation.

Finally the EPAF-Study found that the physiotherapy-led physical activity intervention, which included a supervised exercise component, had a greater impact on physical activity participation than the practice nurse approach of physical activity counselling. However, the populations in each of the study group‘s were different and one cannot therefore conclude that it was a more effective intervention. Consequently, a future research recommendation would be to evaluate the impact of this physiotherapy-led physical activity intervention in community settings such as general practice in high risk individuals. This study would suggest there is added value in the inclusion of a physiotherapist as an integral part of preventive cardiology practice and this should be more formally tested.

Chapter 8: Conclusion

The EUROACTION programme provides a unique model of preventive cardiology, which has been successfully implemented and assessed, and this study's findings would suggest it should be applied in routine clinical practice. The EPAF-Study has demonstrated, supported by objective measurement, that the EUROACTION programme was effective in increasing physical activity participation and cardiorespiratory fitness in people with coronary heart disease and those at high risk of developing cardiovascular disease. Importantly this study has been able to substantiate the subjective measure previously cited in the trial's publication of its results (Wood et al., 2008).

Despite the unselected nature of this patient sample from 12 district hospitals and general practices in Europe, 1 in 2 patients achieved the target for physical activity participation compared to 1 in 5 in standard practice. These self-reported findings are supported in this study's findings by observed differences in step counts equating to an additional mile and half mile a day of walking in coronary patients and individuals at high CVD risk respectively with the difference for coronary patients being statistically significant. There were also trends for increased physical fitness at 1-year in favour of INT in both groups of patients. In INT, over the period of the year, patients' fitness improved on average by 1 MET in coronary patients and 1.5 METs in those at high cardiovascular risk in general practice. These gains represent clinically important improvements in health outcomes.

In the primary analysis at 1-year, the trends in favour of the INT were strongest in the hospital study indicating that a physiotherapy-led physical activity intervention and supervised exercise component were more effective. None the less, the physical activity counselling intervention delivered by nurses in general practice was also associated with clinical meaningful improvements in physical activity participation.

It is important to recognise that in the comparison of INT versus UC at 1-year there were no significant differences observed in cardiorespiratory fitness in both the hospital and general practice parts of the study. For the objective measure of physical activity participation a statistically significant difference was only observed in the hospital study. However, the EPAF-Study illustrates the considerable the effect that heterogeneity has on statistical power. If just one of the pairs of centres moved in favour of UC and to a high enough magnitude the result was a p-value greater than 0.5, despite the fact that the remaining five pairs were all clearly in favour of the INT.

The sample size for this nested study within the main EUROACTION trial was out of the control of the author as this was predetermined. Essentially the EPAF-Study was considerably underpowered due to the clustering of the data and more pairs were needed within each country. Using only one pair of hospitals and one pair of general practices resulted in problems with statistical power as well as limitations to generalisability. There was enormous variation both within and between countries and consequently challenges in interpreting the results.

To illustrate the importance of not solely focussing on the p-value and ensuring to consider the "clinical importance" of each outcome observed, the absolute difference in steps between INT and UC at 1-year was similar in the general practice and hospital study and in both cases exceeded the minimal clinically important difference (MCID), yet this difference was only statistically significant for the latter. Again, whilst differences in cardiorespiratory fitness were not statistically significant they clearly surpassed the MCID.

The physical activity intervention was innovative in that it employed cognitive and motivational techniques, together with early programme commencement, and showed that these approaches effectively increase uptake and programme adherence. EUROACTION has also shown that it is possible to successfully engage the majority of patients with coronary disease and those at high risk of developing CVD in a preventive cardiology programme in settings generalisable to everyday clinical practice. These differences observed of course may be due to chance but given the trend for every result was in favour of the INT and reached the MCID should be considered.

This research makes a distinct and original contribution to knowledge by demonstrating it is possible to raise the benchmark for physical activity participation and fitness in preventive cardiology care for coronary patients, asymptomatic individuals identified at high risk and their partners in everyday clinical practice. However, a sizable population had still not reached the recommended target despite an intensive intervention and consequently there remains the need to explore methods to further increase uptake, programme completion and maximise patient outcomes in preventive cardiology practice. In addition women, older people, people with stable angina and people recruited though a HeartScore> 5% were either less likely to participate or drop-out. There is also a clear need to develop more effective management strategies to target individuals with such characteristics.

There are also important limitations and sources of bias that have been explored within the discussion. Essentially there was no blinding to treatment allocation and patients self-selected introducing a selective sample and possible measurement bias. However, this was also a demonstration programme of a preventive cardiology programme being delivered in every day clinical settings and these types of trials are very difficult to carry out in double blind trials with individual randomisation.

In summarising this study's distinct and original contribution to knowledge:

- These findings add new knowledge on interventions that are effective for people at risk of developing cardiovascular disease and people with established coronary heart disease.
- The difference in physical activity participation was at 1 year; 8 months after completion of the intervention in the hospital study. This highlights the success of this programme in changing physical activity behaviour and its association with sustainable improvements in lifestyle behaviours. This is again a new finding as long-term adherence to a healthy lifestyle remains the one of the most difficult problems in secondary prevention of CVD.
- The results achieved for physical activity participation are better than those in the GOSPEL trial (Giannuzzi et al., 2008) and consequently provide new knowledge in raising the benchmark for the standards of preventive care even further. In EUROACTION UC, the results concur with the control group for the GOSPEL study, indicating that current practice has less impact on physical activity participation in patients with CHD with little change in the proportions achieving the EGPA over the duration of the year and three quarters not meeting these targets. This highlights the need for current practice in cardiac rehabilitation to evolve and the EUROACTION study provides a new model of service delivery that has been shown to be more effective.
- Given the WHO goal to decrease inactivity by 10% these findings support the EUROACTION model as a feasible option to deliver this target. Half of all INT patients were achieving this target as opposed to just over one in five in UC.
- This study concurs with previous authors that self-reported activity tends to be over-reported (Hardman and Stensel, 2009; Sallis and Saelens, 2000). The inclusion of the Yamax Digiwalker SW200 pedometer was used to validate self-reported physical activity which is the most recommended pedometer model for research purposes giving greater confidence in the step count data and this study's validity (Bassett and John, 2010). The study's findings would suggest the public health message of 10,000 or more steps per day

is not appropriate in these populations and should not be routinely applied in preventive cardiology practice.

- Fitness was measured objectively and is subject to far less measurement error and therefore this study gives greater confidence that the EUROACTION programme was effective. The EUROACTION intervention in general practice achieved an increase of 1.5 METs in fitness, which translates to a 12-26% reduction in all-cause mortality (Myers et al., 2002; Gulati et al., 2003). The intervention in the hospital study similarly achieved a 1 MET gain (8-16% reduction in all-cause mortality) (Myers et al., 2002; Gulati et al., 2003).
- This study can inform other cluster-randomised controlled trials of the importance to take clustering of data into account and incorporate the addition of value to account for the size of the clustering and inflate the sample size, known as an intra-class correlation.
- These findings also highlight that this model of care is applicable to current practice and the intervention was specifically delivered in general hospitals and primary care practices as opposed to specialist centres. This study therefore highlights that it is feasible to reconfigure existing services to provide an integrated care approach.

"The EPAF-Study has demonstrated that the EUROACTION programme was effective at increasing physical activity participation but objective measures indicate this is to a lesser degree than the self-reported physical activity outcomes previously published. Clinically important differences in objectively measured physical activity participation and cardiorespiratory fitness suggest further research which is sufficiently powered is warranted."

The EPAF-Study

The EUROACTION Physical Activity and Fitness Study

A paired, cluster-randomised controlled trial in 8 European countries in people with coronary heart disease and individuals at high risk of developing cardiovascular disease

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Brunel University

School of Health Sciences and Social Care

Doctor of Philosophy Thesis

The EPAF-Study

The EUROACTION Physical Activity and Fitness Study

APPENDICES

EuroAction
for our hearts

Appendix 1:

Publication of EUROACTION methodology

European Heart Journal Supplements (2004) **6** (Supplement J), J3–J15

EUROACTION: A European Society of Cardiology demonstration project in preventive cardiology

A cluster randomised controlled trial of a multi-disciplinary preventive cardiology programme for coronary patients, asymptomatic high risk individuals and their families. Summary of design, methodology and outcomes

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KEYWORDS EuroAction; Preventive cardiology; Primary and secondary prevention and rehabilitation of cardiovascular disease

Introduction

There is substantial scientific evidence that professional lifestyle intervention on smoking, diet and physical activity, together with control of blood pressure, cholesterol and glycaemia, and selective use of prophylactic drug therapies (aspirin and other anti-platelet therapies, beta-blockers, ACE inhibitors or A-II receptor blockers, lipid-lowering drugs and anticoagulants) can reduce cardiovascular morbidity and mortality in patients with established coronary disease, and can also reduce the risk of developing atherosclerotic disease in high risk individuals. The joint European Societies guidelines on prevention of cardiovascular disease (CVD) define priorities for preventive cardiology in clinical practice [1]. The first is patients with established atherosclerotic cardiovascular disease. The second is high risk individuals from the general population with hypertension, dyslipidaemia, diabetes, or a combination of these and other risk factors which puts them at high multifactorial risk of developing CVD. The third is the families (first degree blood relatives) of both coronary patients and high-risk individuals.

Although cardiac rehabilitation has traditionally focused on physical rehabilitation this speciality has gradually evolved into comprehensive professional lifestyle programmes – smoking cessation, making healthy food choices and becoming physically active – based on behavioural models of change. Risk factor management in terms of controlling blood pressure, lipids and glucose to defined targets, and the use of prophylactic drug therapies, is also now an integral part of this approach. Finally, the psychosocial and vocational support required to help patients lead as full a life as possible is also provided. This evolution in cardiac rehabilitation is reflected in the current World Health Organisation's definition [2]:

> The rehabilitation of cardiac patients is the sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible physical, mental and social conditions, so that they may, by their own efforts preserve or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form of therapy but must be integrated with the whole treatment of which it forms only one facet.

The overall objective for patients who present with symptoms of coronary artery disease – stable angina, unstable angina or acute MI – is to reduce the risk of a further non-fatal event or death from cardiovascular disease. Cardiac rehabilitation was originally provided only for patients recovering from a myocardial infarction (MI) and those who had coronary

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[1] See the Appendix for the organisational structure of the EuroAction Study Group.

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artery bypass graft (CABG) surgery (or other forms of cardiac surgery). With the more recent emphasis on influencing the underlying causes of atherosclerotic disease patients presenting with all forms of coronary artery disease, including unstable and stable angina, are now being included in cardiovascular prevention and rehabilitation programmes. By addressing lifestyle and risk factor management, and prescribing prophylactic drug therapies, the risk of all cardiovascular events can be reduced in all these patients.

Unfortunately, risk factor management in patients with CHD in Europe is far from optimal. Surveys of clinical practice such as EUROASPIRE I and II (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) have shown that integration of cardiovascular disease prevention into daily practice is inadequate [3-5]. There is still considerable potential to further reduce cardiovascular risk in patients with established CHD as many are not achieving the recommended lifestyle and risk factor goals. The majority of coronary patients in the EUROASPIRE II survey in 15 countries had not been advised to follow a cardiac rehabilitation programme, and less than a third of all patients attended such a programme [6]. The traditions and practice of cardiac rehabilitation in Europe differ substantially between countries, ranging from intensive residential rehabilitation through to ambulatory and home based programmes. They also differ in their patient populations, staffing, management protocols, duration and follow-up. According to the EUROASPIRE II data, whatever form of cardiac rehabilitation was provided for the coronary patients who reported attending such programmes, the majority did not achieve the lifestyle, risk factor and therapeutic goals [6].

EuroAction

EuroAction is a European Society of Cardiology (ESC) demonstration project in preventive cardiology led by specialists from the former Working Group on Epidemiology and Prevention and the Working Group on Cardiac Rehabilitation and Exercise Physiology (now merged to form the new European Association of Cardiovascular Prevention and Rehabilitation) and the Working Group on Nursing, together with the European Heart Network. The aim of EuroAction is to raise standards of preventive cardiology in Europe by demonstrating that the recommended European and national lifestyle, risk factor and therapeutic goals in cardiovascular disease prevention are achievable and sustainable in everyday clinical practice.

Objectives

The objectives of the EuroAction project are:

(1) to demonstrate the process of care and immediate impact of a 16-week specialist nurse led multidisciplinary hospital based cardiovascular prevention and rehabilitation programme on lifestyle, risk factors and therapeutic management of coronary patients and their families;
(2) to demonstrate the process of care and impact of a hospital led preventive cardiology programme for all first degree relatives of coronary patients with premature disease;
(3) to demonstrate the process of care and the longer term impact of this programme for all coronary patients, partners and first degree relatives at 1 year;
(4) to demonstrate the process of care and impact of a specialist nurse led preventive cardiology programme in general practice on management of high risk individuals and their partners at one year.
(5) to follow up all patients with coronary disease, high risk individuals and their partners, and first degree relatives of patients with premature coronary disease for cardiovascular non-fatal events and cardiovascular and all-cause mortality in order to determine the relationship between intervention and event free survival.

Countries

EuroAction is being conducted by the ESC in eight European countries: Denmark, France, Italy, Poland, Spain, Sweden, the Netherlands and the United Kingdom (www.escardio.org/EuroAction).

Study design

EuroAction is a cluster randomised controlled trial with clinical follow-up at 16 weeks and 1 year (hospital arm) and at 1 year only (primary care arm) (Figs. 1a,b).

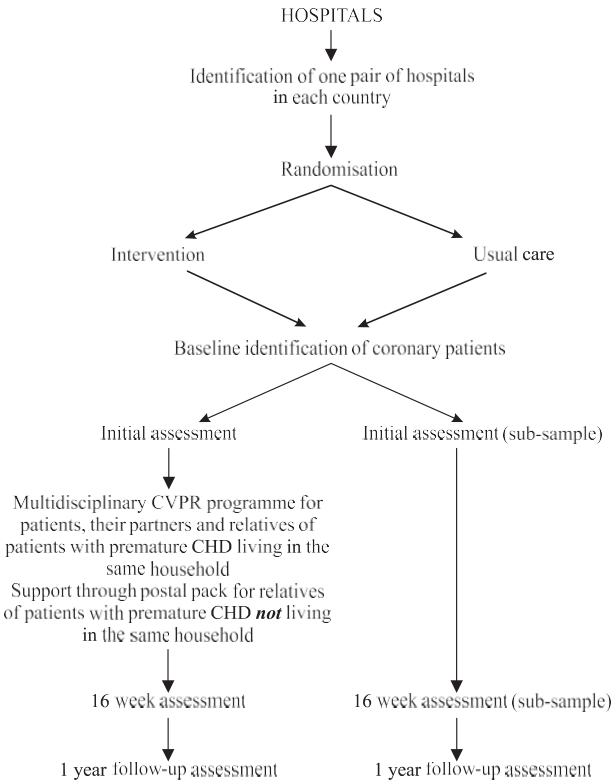

Fig. 1a. Hospital Study Design.

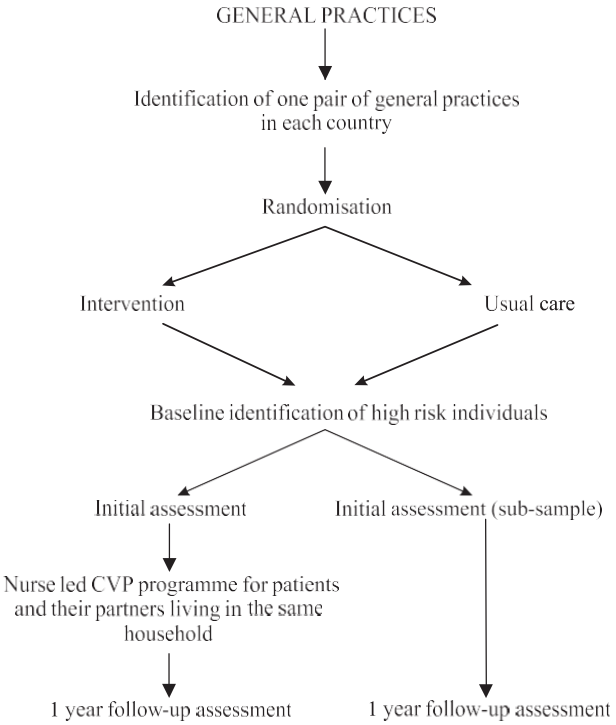

Fig. 1b. Primary Care Study Design.

In each of six countries two district general hospitals (France, Italy, Poland, Spain, Sweden and the United Kingdom), and two general practices (Denmark, Italy, Poland, Spain, the Netherlands and the United Kingdom), have been recruited from different geographical areas. In the hospital centres, all patients with coronary heart disease admitted to the hospitals during 2002 were audited retrospectively in order to assess whether both hospitals were comparable with regard to patients' age, gender and distribution of diagnostic categories. Comparable pairs of hospitals were then randomised within their country pairs to intervention or usual care. In the general practice centres a retrospective audit of the practice populations in terms of patients' age, gender and drug prescriptions was undertaken during 2003. The comparable general practices were then randomised within their country pairs to intervention or usual care.

Study populations

Hospitals

In each hospital the following patients and their families are prospectively identified when they are admitted as in-patients or seen as out patients:

(a) Consecutive patients (men and women) <80 years presenting for the first time (incident cases) as in-patients or out-patients with a consultant diagnosis of coronary artery disease:
  (i) Acute myocardial infarction;
  (ii) Unstable angina;
  (iii) Stable angina.
(b) Partners of all patients.
(c) First degree relatives (siblings and offspring >18 years) of patients with *premature* CHD (men <55 years and women <65 years) living in the same household or elsewhere.

General practices

In each general practice the following patients and their families are prospectively identified when they attend their general practitioner for whatever reason:

(a) Consecutive patients (men and women) >50 years and <80 years with no history of cardiovascular disease who are:
  (i) At high multifactorial cardiovascular risk (HeartScore ≥5% over 10 years, either now or when projected to age 60 years) [7] and on no medical treatment for blood pressure, lipids or diabetes.
  (ii) On treatment with anti-hypertensive and/or lipid-lowering drug therapies started in the last year but with no diabetes.
  (iii) Diagnosed with diabetes mellitus (treated by diet alone or with oral hypoglycaemic drug therapy and/or insulin) within the last three years.
(b) Partners of all patients.

Study patients and families

Coronary patients, partners and families (hospital arm): In intervention hospitals patients are recruited to a nurse led multidisciplinary cardiovascular prevention and rehabilitation (CVPR) programme which aims to achieve the recommended lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention. The partners of coronary patients and first degree blood relatives of patients with premature coronary heart disease (men <55 years and women <65 years) living in the same household are also identified and invited to attend the cardiovascular prevention and rehabilitation programme in order to achieve the same lifestyle, risk factor and therapeutic goals. Those first degree blood relatives of patients with premature coronary disease *not* living in the same household are supported through a postal relatives pack. In usual care hospitals, coronary patients are identified and a random sub-sample screened at baseline, but they do not receive any form of special support. The partners of coronary patients in usual care are not contacted at baseline.

Re-screening of coronary patients, their partners and blood relatives of patients with premature coronary disease living in the same household from intervention hospitals takes place at 16 weeks, to assess lifestyle, risk factor control and use of drug therapies. Re-screening of the same random sub-sample of usual care coronary patients (but not their partners) also takes place at 16 weeks.

Re-screening of all coronary patients, their partners and first degree blood relatives of patients with premature coronary disease living in the same household, both in intervention and usual care, takes place at 1 year to assess lifestyle, risk factor control and use of drug therapies. The relatives of patients with premature

coronary disease *not* living in the same household from both intervention and usual care hospitals are followed up by postal questionnaire at 1 year to assess what action has been taken, and with what results, in relation to lifestyle, risk factor and therapeutic management. All patients, partners and blood relatives of patients with premature coronary disease are followed up for major cardiovascular events, and cardiovascular/total mortality.

High risk individuals and partners (primary care arm): In general practices high risk patients are recruited to a nurse led multidisciplinary cardiovascular prevention programme which aims to achieve the recommended lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention.

Individuals at high cardiovascular risk are identified opportunistically in the following way:

(a) Men and women 50 years of age or older, but less than 80 years who are found to be at high multifactorial risk: Men with at least 1 (women with at least 2) cardiovascular risk factor(s) (smoking and/or raised blood pressure, i.e. ≥140/90 mmHg, and/or raised total cholesterol, i.e. ≥5 mmol/l (190 mg/dl) currently on no medication for arterial hypertension and/or dyslipidaemia, and who are found to be at high multifactorial risk when screened by the nurse: CVD risk ≥5% over 10 years (now or projected to age 60 years), according to the HeartScore risk estimation system (www.escardio.org/HeartScore).
(b) Men and women in the same age range, who have been started on treatment in the last year with antihypertensive and/or lipid-lowering therapies but with no diabetes.
(c) Men and women in the same age range, who have been diagnosed in the last 3 years with diabetes and are under treatment with diet, oral hypoglycaemics and/or insulin regardless of treatment for hypertension and dyslipidaemia.

In intervention general practices a cardiovascular prevention (CVP) programme is delivered by specialist nurses supported by the HeartScore risk assessment and management software programme and EuroAction educational materials. The object is to achieve national and European lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention. The partners of high risk individuals living in the same household are identified and supported through the same programme and screened at the end of the programme.

In usual care practices high risk individuals are identified in the same way and a random sub-sample screened at baseline, but they do not receive any form of special care. The partners of high risk individuals in usual care are not contacted at baseline.

All high risk individuals and their partners, both in intervention and usual care, are followed up and screened at 1 year to assess lifestyle, risk factor control and use of drug therapies. All patients and partners of high risk individuals are followed up for major cardiovascular events, and cardiovascular/total mortality.

The Preventive Cardiology Programme

The Cardiovascular Prevention and Rehabilitation (CVPR) Programme (hospital arm)

Aim

The EuroAction CVPR programme is a comprehensive, multi-disciplinary, hospital based sixteen-week programme for coronary patients and their families. The aim of the programme is to help coronary patients and their partners, and first degree relatives of patients with premature coronary disease, to achieve the European lifestyle, risk factor and therapeutic goals as defined in the 1998 Joint European Societies' guidelines (Table 1) [8].

The programme is co-ordinated by a specialist cardiac nurse. In each hospital, the team is made up of two cardiac specialist nurses, a dietitian, and a physiotherapist supported by a lead cardiologist. These core disciplines facilitate lifestyle change in relation to smoking, diet and physical activity. However, other disciplines are involved as required,

Table 1
European lifestyle, risk factor and therapeutic targets

- Giving up smoking
- Eating a healthy diet
- Becoming physically active
- Achieving and maintaining a healthy shape (waist circumference below 94 cm [below 37 inches] for men and below 80 cm [below 31.5 inches] for women) and weight (Body Mass Index below 25 kg/m^2)
- Blood pressure *below* 140/90 mmHg (for those with diabetes *below* 130/80 mmHg)
- Total cholesterol *below* 5.0 mmol/l [*below* 190 mg/dl] (LDL cholesterol *below* 3.0 mmol/l [*below* 115 mg/dl])
- Blood glucose *below* 6.1 mmol/l (*below* 110 mg/dl) and good glycaemic control in all persons with diabetes
- To ensure that *each* of the following classes of cardio-protective medications are prescribed as clinically indicated, at the doses used in the clinical trials, for all coronary patients and to encourage long term compliance with these therapies:
  - Anti-platelet therapy
  - Beta-blockers
  - ACE inhibitors or A-II receptor blockers
  - Lipid lowering therapy (statins)

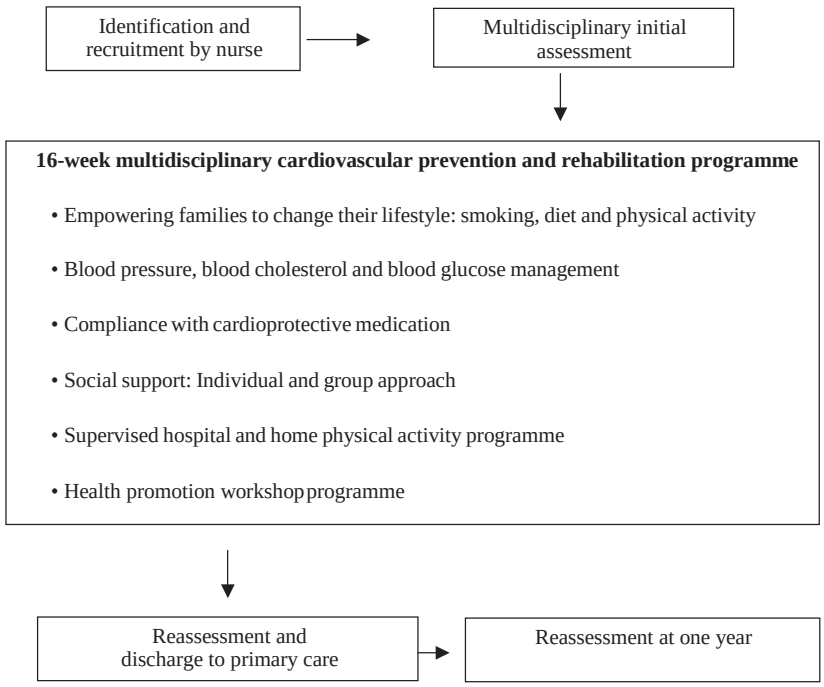

Fig. 2. The process and delivery of care for the hospital CVPR programme.

for example pharmacists, clinical psychologists, and occupational therapists. The lead cardiologist works closely with the specialist nurses to ensure patients and families achieve the blood pressure, cholesterol and diabetes targets. The cardiologist prescribes and up-titrates cardioprotective medications.

Family approach

The nurse proactively identifies newly diagnosed coronary patients and recruits them to the CVPR programme (Fig. 2). As the programme is family based, the partners of all coronary patients, and first degree relatives of patients with premature coronary disease (men <55 years and women <65 years) are also recruited to the programme. Partners of patients who present with coronary disease are at higher risk of developing cardiovascular disease than the general population [9], because of a common lifestyle and shared cardiovascular risk factors. In addition, first degree relatives of patients with premature coronary disease are at particularly high risk, in part for the same reasons but also because some families have inherited dyslipidaemias, e.g. family hypercholesterolaemia, resulting in premature atherosclerotic disease. So when coronary disease develops it is appropriate to offer lifestyle and risk factor management to the whole family, not just the coronary patient.

Initial family assessment

The initial assessment of the family is by the whole multi-disciplinary team and forms the starting point for the intervention. The nurse explains the nature of the diagnosis and the causes of atherosclerosis, and the three disciplines carry out a full assessment of cardiovascular risk, and discuss a family plan for reducing risk. This assessment of patients, partners and relatives includes smoking habit, diet and physical activity; measurement of body mass index (BMI), waist circumference, blood pressure, fasting cholesterol and glucose. Medications are recorded and compliance is assessed. Health beliefs, anxiety and depression, illness perception and mood are also assessed with self-administered questionnaires [10-18]. Health-related quality of life is also assessed [19].

Each patient and family member is given a *Personal Record Card*, which is pocket sized but folds out to an A4 sheet. Lifestyle and risk factor goals are summarised and progress is recorded as well as medications and appointments (www.escardio.org/EuroAction). All families are given a *Family Support Pack* which reinforces the information provided by the team at the initial assessment and at the subsequent health promotion workshop and exercise sessions (www.escardio.org/EuroAction). It provides contact details of the nurse, describes the family approach to the programme, and contains information cards on smoking, diet, physical activity and weight management, blood pressure, cholesterol and diabetes. The pack provides information about coronary disease, cardiac investigations and procedures and cardioprotective medications.

The lifestyle intervention

Coronary patients and their families require integrated, multidisciplinary support to achieve appropriate lifestyle change: quitting smoking, making healthier food choices, achieving a healthy weight and shape, and increasing physical activity – based on behavioural models of change. Families work together to achieve

Table 2
The European recommendations for dietary intake

(a) Goals for which scientific evidence is strong and public health gain large
  (1) Saturated fat and Trans fats:
    (i) Less than 10% of dietary energy from saturated fat
    (ii) Less than 2% of energy from trans fats
  (2) Fruit and Vegetables: More than 400 g/day
  (3) Salt: Less than 6 g/day
  (4) Obesity and overweight:
    (i) BMI < 25 kg/m^2
    (ii) PAL of more than 1.75 [a]
(b) Goals for which scientific evidence is moderate and public health gain moderate
  (1) Total fat: Less than 30% of total energy
  (2) Polyunsaturated fat:
    (i) N-6 polyunsaturated fat: 4–8% energy
    (ii) N-3 polyunsaturated fat: 2 g/day of linolenic acid and 200 mg/day of very long chain fatty acids
(c) Goals for which scientific evidence is weaker and public health gain smaller
  (1) Dietary fibre: more than 25 g/day (or 3 MJ) of dietary fibre and more than 55% of energy from complex carbohydrates
  (2) Folate from food: more than 400 mg/day
  (3) Sugary foods: four or fewer occasions per day

[a] Physical Activity Level (PAL) is the ratio of total energy expenditure to estimated basal metabolic rate. A PAL of 1.75 is equivalent to 60 minutes/day of moderate activity or 30 minutes/day of vigorous activity.

Table 3
Dietary assessment

Characteristic	Assessment
Intake of specific cardioprotective foods within the Mediterranean diet	Food Habit Questionnaire
Percentage energy from macro-nutrients	Macronutrient dietary analysis of 2 × 24 hour recalls

lifestyle changes and support each other in sustaining them over a lifetime. Involving the patient's partner, and other family members sharing the same household, in making behavioural change is more likely to be successful than treating the patient in isolation [20].

The multidisciplinary team uses a common approach to lifestyle change in patients and families. This is based on the *stages of change model* proposed by Prochaska and DiClemente [21] which recognises that individuals are not equally ready to change their behaviour at a given point in time. Those who are ready and motivated are more likely to change. The team draws on various methods to increase motivation, overcome barriers and develop strategies. For example, motivational counselling [22] can provide a way to work with ambivalence, to increase motivation and self-efficacy, to set goals and to create a management plan.

The programme provides both group and one to one support which comes from three sources: the family; other people attending the programme; and the health professionals.

(i) *Smoking cessation*. The aim is to help patients and families stop smoking completely.

The nurse assesses current smoking status, health beliefs regarding tobacco smoking, history of tobacco smoking, and previous quit attempts in patients, partners and relatives. Breath carbon monoxide is recorded using a Smokerlyser (Bedfont micro-smokerlyser, Bedfont Scientific, Model EC 50 Micro III).

The person's stage of change is assessed in relation to smoking behaviour and the level of dependence on nicotine using the 'Fagerstro¨m test for nicotine dependence' [23–25]. These results inform the level of support and follow up required, and the need for pharmacological therapy to manage nicotine withdrawal.

The nurse helps the person to prepare for a quit attempt, sets a quit date and makes contingency plans in the event of a relapse. The cardiologist is asked to prescribe nicotine replacement therapy or other drug therapy if appropriate.

In summary, the nurse motivates and helps those who are ready to quit, monitors the pre-contemplators and contemplators who are not yet ready, provides maintenance and follow up to those who are attempting to quit, and ensures pharmacological support where appropriate.

(ii) *Dietary intervention*. The aim is to give professional advice on food and food choices to compose a diet associated with the lowest risk of cardiovascular disease (Table 2).

The dietitian assesses knowledge and attitudes to diet, and measures dietary intake in patients and their families using the instruments shown in Table 3. The Food Habit Questionnaire is administered using a structured interview method to assess food intake. It contains 12 questions and incorporates information about frequency and quantity of 98 food/alcohol items including the

Table 4
Physical activity assessment

Characteristic	Assessment
Habitual physical activity patterns	7-day activity recall interview International Physical Activity Questionnaire (IPAQ) Number of steps per day (DIGI-WALKER^{TM} SW-200 pedometer)
Functional capacity (Hospital)	Incremental Shuttle Walk Test (ISWT) ECG Exercise tolerance tests where available
Functional Capacity (Primary Care)	Chester step test
Functional limitations	Functional limitations profile score of the short form 36 questionnaire (SF-36)

food groups: fruit and vegetables, fish, types of fats and alcohol. This questionnaire is validated against a seven day diet diary.

Weight and height are measured using standardised equipment (Seca 707 digital scales with measuring stick), and BMI is calculated using the formula weight (kg)/height (m^2). A waist measurement is taken using a standardised method [26]. The healthy body mass index (BMI) range is 18.5–24.9, and waist circumference should be less than 102 cm for men, and less than 88 cm for women [1].

In a random sub-sample of families, a macronutrient dietary analysis is undertaken based on two 24-hour dietary recalls. The dietitian follows a standardised method of 'Explicit food description' which uses the general content of facets and descriptors [27]. In this way, the dietitians working in different cultural settings can describe food in the same way, ask the same sequence of questions, and record answers in the same way.

As the lifestyle intervention is family based, the dietitian addresses the main person in the household responsible for buying and preparing food, and advises the whole 'family' rather than an 'individual' on their own. The dietitian translates the recommendations in Table 2 into practical advice which is individualised to family members. Advice is given in terms of food (not nutrients) and patterns of eating. This advice is adapted for the specific needs of each individual by taking account of factors such as weight, hypertension, dyslipidaemia and diabetes.

Dietary goals are set which are realistic and achievable depending on stage of change. For example, for weight management, the dietitian may set an initial goal of 10% weight loss, if the healthy BMI range is unrealistic in the short term [28].

The dietitian sees patients and families on a weekly basis. By attending the weekly health promotion workshop and exercise sessions, the dietitian is available to provide advice as required. The dietitian organises the healthy eating and weight management workshop. The dietitian also advises on local facilities available in the community to provide support to families.

(iii) *Physical activity intervention*. The aim is to help patients and families to increase their physical activity safely to the level associated with the lowest risk of CVD. The advice is to choose enjoyable activities which fit into people's daily routine, preferably 30–45 min, 4–5 times weekly at 60–75% of the average maximum heart rate.

The physiotherapist assesses habitual physical activity, functional capacity and other factors in patients and families using the instruments described in Table 4. The 7-day Activity Recall provides an estimate of habitual physical activity [29] according to the Caspersen & Powell activity and Schoenborn activity classification systems [30]. A random sub-sample of families are assessed using the International Physical Activity Questionnaire (IPAQ) [31]. The DIGI-WALKER^{TM} SW-200 pedometer [32] is used as an objective marker of current levels of physical activity. Functional capacity is measured using the Incremental Shuttle Walk Test (ISWT) [33] which also provides information on heart rate response and rating of perceived exertion at given workloads.

The physiotherapist develops an individual physical activity plan with realistic goals for each family member based on stage of change.

Every week for eight weeks, the physiotherapist leads a progressive endurance exercise training programme, which is group based. This exercises individuals between 60% and 75% of a predetermined asymptomatic maximum heart rate. The programme is intentionally not equipment based so it can be used at home. Patients gain the ability to sustain and self-regulate safe and effective physical activity levels.

The individualised physical activity plan for each family member follows the hospital based exercise prescription. In addition, the step-counter (DIGI-WALKER^{TM} SW-200 pedometer) is used as a motivational tool. Targets are set and reviewed every week. The total physical activity prescription aims to achieve the European recommendations for each individual as well as equipping families with the necessary knowledge and skills to maintain their physical activity levels safely and effectively in the longer term.

Managing patients and families to target blood pressure, cholesterol, and glucose

The aim is to bring the blood pressure, blood cholesterol

Table 5
Health promotion workshop topics in the hospital CVPR programme

(1) Information about coronary heart disease and cardiac procedures
(2) Understanding cardiovascular risk:
(a) Adopting healthy lifestyle habits to reduce cardiovascular risk
(i) Smoking and cardiovascular disease
(ii) Healthy eating: choosing the right foods
(iii) Benefits of physical activity
(b) Other risk factors: Blood pressure, blood cholesterol and blood glucose: how lifestyle change and medication help
(3) Understanding cardioprotective medications
(4) Living with coronary heart disease:
(a) Recovering from cardiac events and procedures
(b) Sexual activity and CHD
(c) Returning to work
(5) Coping emotionally with coronary heart disease:
(a) Managing stress and learning how to relax
(b) Anxiety and depression – positive thinking

and blood glucose of all patients, partners and first degree relatives to below target levels.

The nurse and cardiologist are responsible for the management of blood pressure, cholesterol and glucose.

The European target for blood pressure is *<140/90 mmHg (130/80 mmHg in diabetes)*. The blood pressure is measured at the initial assessment, and the nurse consults the cardiologist if it is above target level. The cardiologist initiates or up-titrates medication as appropriate. The nurse measures the blood pressure at weekly intervals during the programme. Once drug treatment is started, weekly monitoring continues until the blood pressure is reduced below target.

The European target for total cholesterol in EuroAction is *<5.0 mmol/l (190 mg/dl)*. The total cholesterol is measured at the initial assessment. If the cholesterol is above the target level, a statin is prescribed if it has not already been started. The blood cholesterol is monitored monthly until target is reached. The cardiologist up-titrates treatment if required.

The European target for fasting blood glucose is *<6.1 mmol/l (110 mg/dl)*. A fasting and random glucose are measured at the initial assessment. An oral glucose tolerance test is performed if the fasting glucose is ≥6.1 mmol/l (110 mg/dl) to diagnose diabetes or impaired glucose tolerance. Patients and other family members diagnosed with diabetes or impaired glucose tolerance are managed according to the diabetic target for blood pressure, as well as the cholesterol and glycaemic targets defined above. People who are diagnosed with diabetes are also referred to the diabetologist.

The nurse checks that all appropriate cardioprotective medications are prescribed; antiplatelet therapy; beta-blockers; ACE inhibitors/Angiotensin II receptor blockers; and lipid-lowering drugs. The nurse checks the dose of these drugs to make sure they are evidence based. The nurse liaises with the cardiologist to initiate a prescription or up-titration of these medications. The nurse also provides education and information to patients and families about their medications to facilitate compliance.

The Health Promotion Workshop Programme: The nurse coordinates an eight week rolling programme of workshops which include the topics listed in Table 5. The workshops are part of the weekly meetings which bring patients and families together. They are an important part of the group support provided by the programme. The workshops are designed to be interactive, informative and to provide an open forum for discussion.

Reassessment: On completion of the programme the patient and family are reassessed for lifestyle, risk factor and therapeutic management. The results of this sixteen-week assessment are sent to the person's own physician to encourage continuation of appropriate treatment in the long term. A final reassessment takes place one year after identification.

The Personal Support Pack: for first degree relatives of patients with premature coronary disease

The first degree relatives (siblings or offspring over the age of 18) of patients who present with premature coronary disease (men who present with CHD before the age of 55 and women before the age of 65) are identified by the nurse. Relatives who live in the same household as the index patient are recruited to the programme. Those relatives who do not live in the same household as the patient are sent a *Personal Support Pack* in the post (www.escardio.org/EuroAction).

This pack comprises a covering letter, an educational booklet, a questionnaire, and a letter to the relative's own physician. The booklet provides information on coronary disease and cardiovascular risk, and advice on how to adopt a healthy lifestyle. The questionnaire has two sections. Section 1 is completed by the relative and includes questions on their current lifestyle regarding smoking, diet and physical activity. Section 2 is for the relative's physician, who is asked to measure and record body mass index, waist circumference, blood pressure and blood cholesterol, and to record medications. The physician is requested to manage the relative to the lifestyle and risk factor targets.

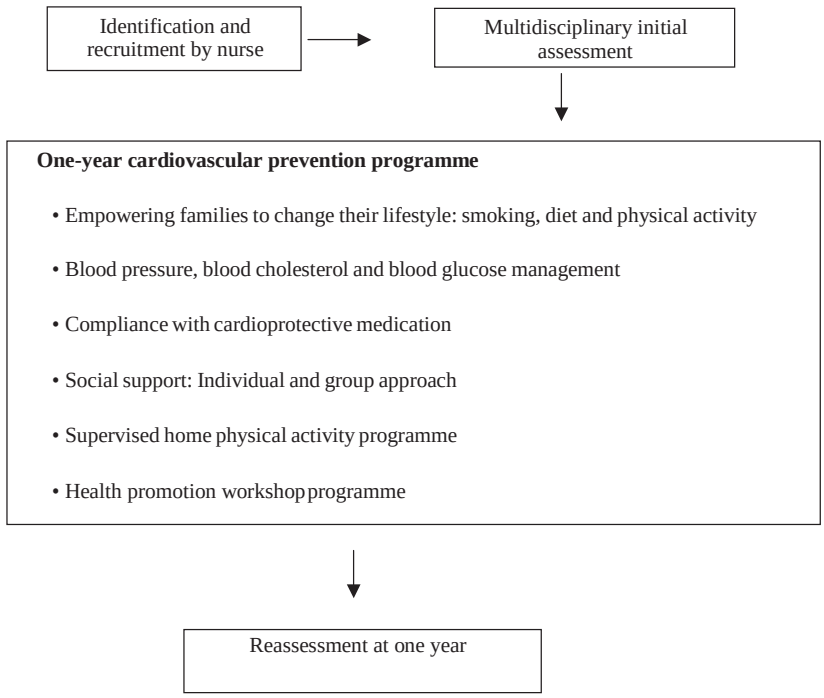

Fig. 3. The process and delivery of care for the primary care CVP programme.

A follow up questionnaire is sent to relatives one year later to evaluate lifestyle, risk factor and therapeutic management.

The Cardiovascular Prevention (CVP) Programme (primary care arm)

Aim

The EuroAction CVP primary care programme is based on the same principles as the hospital CVPR programme, particularly in relation to the family based approach and lifestyle management. It is a comprehensive multifactorial one-year programme for individuals at a high risk of developing cardiovascular disease and their partners. The aim of the programme is to help high risk individuals and their partners to achieve the European lifestyle, risk factor and therapeutic targets as defined in the Joint European Societies' guidelines (Table 1) [8].

The programme is co-ordinated by a specialist cardiac nurse. In each practice, the team is made up of one cardiac specialist nurse, and the general practitioners (GP) working in the practice. The nurse is specially trained to address smoking, diet and physical activity. However, the nurse can refer to other disciplines as required. The GPs work with the specialist nurse to ensure that patients and their partners achieve the blood pressure, cholesterol and glucose targets. The GPs prescribe and up-titrate cardioprotective medications.

Family approach

The nurse proactively identifies high risk individuals and recruits them to the CVP programme along with their partners (Fig. 3).

Initial family assessment

The initial assessment of the family by the nurse is the starting point for the intervention. The nurse explains the concept of cardiovascular risk, carries out a full assessment of risk, and discusses a family plan for reducing risk. This assessment of patients and their partners includes smoking habit, diet and physical activity; measurement of BMI, waist circumference, blood pressure, fasting cholesterol and glucose. Medications are recorded and compliance is assessed. Health beliefs, anxiety and depression, illness perception and mood are also assessed with self-administered questionnaires [10–18]. Health-related quality of life is also assessed [19].

Each family member is given a *Personal Record Card* and a *Family Support Pack* (www.escardio.org/EuroAction).

The lifestyle intervention

The family approach to lifestyle intervention is the same as the hospital CVPR programme. The nurse is trained to address all three elements of lifestyle change: stopping smoking, making healthier food choices, achieving a healthier weight and shape, and increasing physical activity, based on a behavioural model of change.

Functional capacity is measured with the *Chester step test* [34] and not the Incremental Shuttle Walk Test. The nurse does not lead a formal exercise training programme, but encourages a home physical activity programme, and the use of appropriate facilities in the community.

Managing patients and families to target blood pressure, cholesterol, and glucose

The aim is to bring the blood pressure, blood cholesterol

Table 6
Health promotion workshop topics for the primary care CVP programme

(1) Understanding cardiovascular risk:
(a) Adopting healthy lifestyle habits to reduce cardiovascular risk
(b) Smoking and cardiovascular disease
(c) Healthy eating: choosing the right foods
(d) Benefits of physical activity
(e) Other risk factors: Blood pressure, blood cholesterol and blood glucose: how lifestyle change and medication help
(2) Understanding cardioprotective medications
(3) Coping emotionally:
(a) Managing stress and learning how to relax
(b) Anxiety and depression – positive thinking

and blood glucose of all patients and partners to below target levels. The nurse and GP are responsible for management of blood pressure, cholesterol and glucose.

The European target for blood pressure is *<140/90 mmHg (130/80 mmHg in diabetes)*. The blood pressure is measured at baseline, and if it is above target level, the nurse follows a management protocol. The GP initiates or up-titrates medication as appropriate.

The European target for total cholesterol in EuroAction is *<5 mmol/l (190 mg/dl)*. The total cholesterol is measured at the initial assessment and if it is above target level, the nurse follows a management protocol. The GP initiates or up-titrates medication as appropriate.

The European target for blood glucose is *<6.1 mmol/l (110 g/dl)*. A fasting and random glucose are measured at the initial assessment. High risk individuals and partners diagnosed with impaired fasting glycaemia or diabetes are managed according to the diabetic target for blood pressure, as well as the cholesterol and glycaemic targets defined above. People who are diagnosed with diabetes are also referred to the diabetologist.

The nurse checks that all appropriate medication is prescribed, especially antiplatelet therapy, anti-hypertensives, and lipid-lowering drugs. The nurse checks the dose of these drugs to make sure they are evidence based. The nurse liaises with the GPs to initiate a prescription or up-titration of these medications. The nurse also provides education and information to patients and families about their medications to facilitate compliance.

The Health Promotion Workshop Programme: The nurse coordinates a rolling programme of three workshops which include the topics listed in Table 6. The workshops bring high risk individuals and partners together. They are an important part of the group support provided by the CVP programme. The workshops are designed to be interactive, informative and to provide an open forum for discussion.

Reassessment: One year after identification, the high risk individuals and their partners are reassessed for lifestyle, risk factor and therapeutic management.

Timelines

This demonstration project was planned in 2002. The hospital phase was launched in April 2003 and one-year follow-up results will be available in 2005. The primary care phase was launched in April 2004 and the one-year follow up results will be available in 2006.

Laboratory analyses

Central laboratory analysis of fasting total cholesterol, HDL cholesterol, triglycerides, fasting and random glucose and HbA1c is undertaken in intervention coronary patients at baseline, 16 weeks (hospital only) and 1 year. The same analyses are performed on intervention high risk individuals at baseline and 1 year.

Outcome measures

The analyses for all outcome measures will be at a European level. The six hospital intervention centres will be compared with the six hospital usual care centres at 16 weeks and 1 year, and the six primary care intervention centres will be compared with the six primary care usual care centres at 1 year. The proportions of patients and families achieving the lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention, as summarised in Table 1, will be compared between intervention and usual care for both hospital and primary care. Psychosocial factors will be compared between intervention and usual care for both hospital and primary care. The process and delivery of preventive cardiology care will be described over one year, and compared between intervention and usual care for both hospital and primary care. A health-economic analysis of the preventive cardiology programmes in hospital and primary care will be undertaken. Patients, partners and relatives will continue to be followed up after the first year for major non-fatal cardiovascular events (myocardial infarction and stroke) and cardiovascular/total mortality. A summary of these outcome measures and measurement instruments is given in Table 7.

Statistics

Sample size considerations

A sample size of at least 400 subjects (patients or

Table 7
EuroAction outcomes and research instruments

Outcome measure	Research instrument	Hospitals	Primary care
I. Proportions of patients and family members achieving the lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention:			
Smoking	Self-reported	√	√
	Breath carbon monoxide *(Smokerlyser, Bedfont Scientific, Model EC 50 Micro III)*	√	√
Diet/nutrition	Self-reported	√	√
	Food habit questionnaire	√	√
	24-hour recall	√	
Physical activity	Self-reported	√	√
	Step counter	√	√
	Incremental Shuttle Walk Test *(ISWT)*	√	
	Chester step test		√
	International physical activity questionnaire *(IPAQ)*	√	
	Functional limitation (SF-36 questions)	√	√
Overweight/obesity/ central obesity	Body weight and height *(SECA 707 digital scales with measuring stick)*	√	√
	Waist circumference	√	√
Diabetes	Self-reported medical diagnosis	√	√
	Fasting and random plasma glucose	√	√
	Glycated haemoglobin (HbA1c)	√	√
Blood pressure	Automatic sphygmomanometer *(Omron 711)*	√	√
Blood lipids and glucose	Fasting total cholesterol	√	√
	HDL cholesterol	√	√
	LDL cholesterol (calculated)	√	√
	Triglycerides	√	√
	Fasting and random plasma glucose	√	√
	Glycated haemoglobin	√	√
	Glucose tolerance test	√	
Prophylactic drug therapies	Self-reported	√	√
	- anti-platelet therapies	√	√
	- beta-blockers	√	√
	- ACE- inhibitors	√	√
	- lipid-lowering drugs	√	√
	- anticoagulants	√	√
	- hypoglycaemic drugs	√	√
Other drug therapies	- nicotine replacement and other drug therapies	√	√
	- anti-obesity drugs	√	√
II. Psychosocial			
Depression	Hospital Anxiety and Depression (HAD) Scale	√	√
Compliance	Self-reported	√	
Health beliefs	Health beliefs questionnaire	√	
Risk perception	Risk perception questionnaire		√
Emotional state	Global mood scale	√	
Illness perception	Illness perception questionnaire	√	
III. Process and delivery of care	Recorded and self-reported	√	√
***IV*. Health economics**	EuroQoL questionnaire	√	√
V. Cardiovascular events	Cardiovascular morbidity	√	√
	Cardiovascular/total mortality	√	√

partners or first degree relatives) in both intervention and usual care is needed for detecting differences of at least 10% at the $a = 0.05$ significance level with 80% statistical power in prevalences of lifestyle, other risk factors and use of prophylactic drug therapies at a European level.

Statistical analysis

Descriptive statistics will be used to report lifestyle (smoking habit, diet and physical activity) the prevalences of other risk factors and the use of drug therapies in intervention and usual care groups. Classical univariate and multivariate methods will be applied to statistically evaluate differences between these prevalences.

Appendix: Organisational structure of the EuroAction Study Group

Steering Group

A scientific steering group approved the protocol and the design for this demonstration project in preventive cardiology, and is responsible for the scientific integrity of the trial. The steering group has the following membership: DA Wood (London, UK, Chairman), G De Backer (Ghent, Belgium), D De Bacquer (Ghent, Belgium), M Buxton (Uxbridge, UK), I Graham (Dublin, Ireland), A Howard (Nice, France), K Kotseva (London, UK), S Logstrup (Brussels, Belgium), H McGee (Dublin, Ireland), M Mioulet (Nice, France), K Smith (Dundee, UK), D Thompson (York, UK), T Thomsen (Glostrup, Denmark), T van der Weijden (Maastricht, the Netherlands).

National co-ordinators

The national co-ordinators for each country are also members of the steering committee. They are responsible for identifying and recruiting the hospitals and general practices, obtaining ethics committee approval, appointing and supervising staff in the centres and contributing scientifically to the publication of results. The EuroAction National Co-ordinators and Primary care leaders are as follows:

Denmark: T Thomsen (National Co-ordinator); K Brockelmann (Primary Care leader). France: C Monpe`re (National Co-ordinator). Italy: P Fioretti (National Co-ordinator); A Desideri (Deputy Co-ordinator); S Brusaferro (Primary Care leader). Poland: A Pajak (National Co-ordinator); P Jankowski (Deputy Co-ordinator); T Grodzicki (Primary Care leader). Spain: J De Velasco (National Co-ordinator); A Maiques (Primary Care leader). The Netherlands: T van der Weijden (National Co-ordinator and Primary Care leader). Sweden: J Perk (National Co-ordinator). United Kingdom: DA Wood (National Co-ordinator); J Morrell (Primary Care leader).

Co-ordinating and Data Management Centre

The Co-ordinating and Data management Centre is the Department of Cardiovascular Medicine, National Heart and Lung Institute at Charing Cross Campus, Imperial College, London, UK (Head Professor David Wood). The following staff have specific responsibilities as described: K Kotseva, Senior Clinical Research Fellow; S Connolly, Research Fellow; C Jennings, Study Nurse Co-ordinator; A Mead, Chief Dietician; J Jones, Superintendent Physiotherapist; A Holden, Physical activity Co-ordinator; T Collier, Statistician; M Alston, D Charlesworth, P Homewood, K Pandaya, M Somaia, IT specialists/Data Managers; S Graves, Research Administrator; W Leacock, G Narraway, D Xenikaki, Administrative Assistants.

Central Laboratory

Central Laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose and HbA1c are undertaken by A McLelland, R Birrell and G Beastall in the Department of Pathological Biochemistry, Royal Infirmary, Glasgow (Head of Department J Shepherd).

Statistical Centre

All statistical analyses are undertaken by D De Bacquer, Statistician, from the Department of Public Health (Head of Department G De Backer), Ghent University, Belgium.

Representatives of AstraZeneca

T Bailey, S Burton, A Dean.

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EuroAction
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Appendix 2:

Publication of EUROACTION primary results

Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial

*D A Wood, K Kotseva, S Connolly, C Jennings, A Mead, J Jones, A Holden, D De Bacquer, T Collier, G De Backer, O Faergeman, on behalf of EUROACTION Study Group**

Summary

Background **Our aim was to investigate whether a nurse-coordinated multidisciplinary, family-based preventive cardiology programme could improve standards of preventive care in routine clinical practice.**

Methods **In a matched, cluster-randomised, controlled trial in eight European countries, six pairs of hospitals and six pairs of general practices were assigned to an intervention programme (INT) or usual care (UC) for patients with coronary heart disease or those at high risk of developing cardiovascular disease. The primary endpoints—measured at 1 year—were family-based lifestyle change; management of blood pressure, lipids, and blood glucose to target concentrations; and prescription of cardioprotective drugs. Analysis was by intention to treat. The trial is registered as ISRCTN 71715857.**

Findings **1589 and 1499 patients with coronary heart disease in hospitals and 1189 and 1128 at high risk were assigned to INT and UC, respectively. In patients with coronary heart disease who smoked in the month before the event, 136 (58%) in the INT and 154 (47%) in the UC groups did not smoke 1 year afterwards (difference in change 10·4%, 95% CI −0·3 to 21·2, p=0·06). Reduced consumption of saturated fat (196 [55%] *vs* 168 [40%]; 17·3%, 6·4 to 28·2, p=0·009), and increased consumption of fruit and vegetables (680 [72%] *vs* 349 [35%]; 37·3%, 18·1 to 56·5, p=0·004), and oily fish (156 [17%] *vs* 81 [8%]; 8·9%, 0·3 to 17·5, p=0·04) at 1 year were greatest in the INT group. High-risk individuals and partners showed changes only for fruit and vegetables (p=0·005). Blood-pressure target of less than 140/90 mm Hg was attained by both coronary (615 [65%] *vs* 547 [55%]; 10·4%, 0·6 to 20·2, p=0·04) and high-risk (586 [58%] *vs* 407 [41%]; 16·9%, 2·0 to 31·8, p=0·03) patients in the INT groups. Achievement of total cholesterol of less than 5 mmol/L did not differ between groups, but in high-risk patients the difference in change from baseline to 1 year was 12·7% (2·4 to 23·0, p=0·02) in favour of INT. In the hospital group, prescriptions for statins were higher in the INT group (810 [86%] *vs* 794 [80%]; 6·0%, −0·5 to 11·5, p=0·04). In general practices in the intervention groups, angiotensin-converting enzyme inhibitors (297 [29%] INT *vs* 196 [20%] UC; 8·5%, 1·8 to 15·2, p=0·02) and statins (381 [37%] INT *vs* 232 [22%] UC; 14·6%, 2·5 to 26·7, p=0·03) were more frequently prescribed.**

Interpretation **To achieve the potential for cardiovascular prevention, we need local preventive cardiology programmes adapted to individual countries, which are accessible by all hospitals and general practices caring for coronary and high-risk patients.**

Funding **European Society of Cardiology through an unconditional educational grant from AstraZeneca.**

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See **Comment** page 1973

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Introduction

The scientific evidence for cardiovascular disease prevention is compelling;[1] it shows that lifestyle intervention, risk factor management, and cardioprotective drugs can reduce cardiovascular morbidity and mortality in patients with established atherosclerotic disease and those at high risk (Systemic COronary Risk Evaluation [SCORE]) of developing the disease.[1,2] However, results of risk factor management in patients with coronary heart disease in the European Action on Secondary and Primary prevention through Intervention to Reduce Events (EUROASPIRE)[3–5] study showed that cardiovascular disease prevention in routine clinical practice is inadequate. Most patients are not referred to a cardiac rehabilitation programme and less than a third attend.[6] The EUROASPIRE[4,5] survey in 2000 described the management of coronary patients as a "collective failure of medical practice". The EUROACTION model was developed by the European Society of Cardiology to help patients with coronary heart disease, high multifactorial risk, and diabetes outside specialist cardiac rehabilitation centres to achieve the lifestyle, risk factor, and therapeutic targets defined in the prevention guidelines in routine clinical practice.[7] The aim of this

***Panel:* Primary endpoints**

Goals

Smoking

- Not smoking

Diet

- Saturated fat <10% of total dietary energy per day
- Fruit and vegetables >400 g per day
- Fish >20 g per day
- Oily fish >3 times a week
- Alcohol <30 g per day

Anthropometry

- Body-mass index <25 kg/m^2
- Waist circumference: for women ≤80 cm; for men ≤94 cm

Physical activity

- 30–45 min of moderate intensity physical activity 4–5 times a week

Blood pressure

- <140/90 mm Hg (<130/85 mm Hg in people with diabetes)

Blood cholesterol

- Total cholesterol concentrations <5·0 mmol/L
- LDL cholesterol concentrations <3·0 mmol/L

Blood glucose and diabetes

- Blood glucose concentrations <6·1 mmol/L
- Good glycaemic control in patients with diabetes (haemoglobin A_{1c} <7%)

Cardioprotective drug management

Cardioprotective medications are prescribed as clinically indicated, at doses used in clinical trials for all coronary heart disease and high-risk patients.

- Antiplatelet drugs
- β blockers
- Angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers
- Lipid-lowering drugs (statins)

study was to assess whether a nurse-coordinated, multidisciplinary, family-based, ambulatory, preventive cardiology programme (EUROACTION) in hospital and general practice could increase the proportions of patients and their families achieving the goals for cardiovascular disease prevention compared with usual care (panel).[8]

Methods

Study population

A matched, paired cluster-randomised controlled trial (figure 1) was done in 12 (six pairs) general hospitals in France, Italy, Poland, Spain, Sweden, and the UK, and 12 (six pairs) general-practice centres in Denmark, Italy, Poland, Spain, the Netherlands, and the UK. Hospitals and primary-care centres were randomly assigned to intervention or usual care. The trial started in April, 2003, and was completed in September, 2006.

Consecutive patients (men and women) were prospectively identified. Hospital patients were less than 80 years of age and had coronary heart disease—ie, acute coronary syndromes or exertional angina. Patients in general practice were at least 50 years of age and less than 80 years of age with no history of cardiovascular disease but at high risk of cardiovascular disease (SCORE ≥5% during 10 years, either now or when projected to age 60 years) and not on any treatment; or were on treatment with antihypertensive or lipid-lowering drugs, or both, started in the past year, and no history of diabetes mellitus; or were diagnosed with diabetes mellitus within the past 3 years. Exclusion criteria for all patients in the hospitals and general-practice centres were severe heart failure, severe physical disability, or dementia.

Written informed consent was obtained from all patients and their partners, and ethics approval was obtained from the local ethics committee for each centre.

Study design

In the hospital intervention group, all eligible patients with coronary heart disease and their partners were invited for a nurse assessment of lifestyle, risk factors, and drug treatment. In the hospital usual-care group, a randomly selected subsample (18%) of eligible patients with coronary heart disease, but not their partners, had baseline assessments (figure 1). All eligible patients and their partners in the hospital intervention group were invited for reassessment at 16 weeks, together with the same subsample of patients in the usual-care group. All identified patients with coronary heart disease and their partners in the hospital intervention and usual-care groups were invited for reassessment at 1 year (figure 1).

In the general-practice intervention group, all eligible high-risk individuals and their partners were invited for a nurse assessment of lifestyle, risk factors, and drug treatment. In the usual-care group, a randomly selected subsample (332 [29%]) of high-risk individuals, but not their partners, had baseline assessments (figure 1). All identified high-risk individuals and their partners in the intervention and usual-care groups were invited for reassessment at 1 year (figure 1).

The EUROACTION preventive cardiology intervention programme in hospital and general practice

In the hospitals, cardiologists and nurses recruited eligible patients and their families. After a multidisciplinary assessment of lifestyle, risk factors, and drug treatment by a nurse, dietitian, and physiotherapist, couples attended at least eight sessions—one every week—in which they were assessed by each member of the team (nurse, dietitian, and physiotherapist). The patients and their partners then attended a group workshop and a supervised exercise class. The cardiologists initiated and uptitrated the cardioprotective drugs and the nurses monitored risk factors and adherence to drug treatments at each session. At 16 weeks, patients and their partners were reassessed by the whole team and a report was sent to their family doctors.

In the general-practice centres, family doctors and nurses recruited patients and their families. The programme started with the same nurse assessment of lifestyle, risk factors, and drug treatment as for the hospital patients but was open ended. At each visit—one every week—couples were assessed by the nurse—who led the group workshops—and by the family doctors responsible for drug treatment. The patients and their partners did not have supervised exercise classes.

Patients in the hospital and general-practice centres were assessed for family lifestyle, risk factors, medications, health beliefs, anxiety and depression, illness perception, and mood.[9–15] Patients were provided with a personal record card for lifestyle and risk factor targets and their families with family support packs.

The panel shows the primary outcome measures. In the hospitals, patients were encouraged to achieve a healthy lifestyle with support from their families, other people attending the programme, and the health professionals—ie, hospital nurses, dietitians, and physiotherapists—who used stages of change[16] and motivational interviews.[17] In the general-practice centres, the nurses assessed and managed lifestyle by the same behavioural approaches as those used in the hospitals.

To help all smokers in the family to quit tobacco completely, the nurses assessed the present smoking status, health beliefs, and history of tobacco smoking, and previous attempts to quit. Nicotine dependence was assessed with the Fagerstrom test.[18–21] The nurse helped smokers to prepare for an attempt to quit, set a date, and made contingency plans for a relapse. For those who had already stopped smoking, the aim was to prevent a relapse. Cessation of smoking was self reported and validated by a breath carbon monoxide concentration of less than 6 parts per million.

To achieve a healthy family diet associated with the lowest risk of cardiovascular disease, patients and their families' knowledge and attitudes to diet were assessed by the dietitian (in hospital) or nurse (in general practice). The food-habit questionnaire (validated against a 7-day diet diary)[22] was administered by structured interview to assess food intake. Weight, height, and waist circumference were measured and body-mass index (BMI) was calculated (weight [kg] per height [m^2]).[23] In a randomly selected subsample of families in the hospital programme, the dietitians undertook a macronutrient dietary analysis based on two 24 h dietary recalls with a standardised method of explicit food description,[24] so that food from different cultural settings could be described in the same way.

The dietitians (in hospital) or nurses (in general practice) gave advice in terms of food (not nutrients) and patterns of eating for the family and set realistic goals for patients and their families. For individuals with a BMI of 25 kg/m^2 or more, the initial goal was a weight loss of at least 5% during 1 year. The dietitians saw family members individually at each attendance, organised the healthy eating and weight management workshop, and advised on local community facilities.

To achieve a 30–45 min of moderate intensity activity, four to five times a week as a family, the physiotherapist (in hospital) or nurse (in general practice) assessed habitual and physical activity patterns, functional capacity, and other factors that affected activity participation by families. The 7-day activity recall diary provided an estimate of participation in physical activity.[25] A physical activity plan for the family was developed with realistic goals. In the hospital, the physiotherapist interviewed families individually at each attendance to review goals, and led a group-based progressive endurance exercise training programme once a week. Individuals exercised at 60–75% of a predetermined asymptomatic maximum heart rate. The programme was not equipment-based, so it could be followed in the community and families were provided with a home-based exercise and physical activity plan. In general practice, a physical activity plan was developed in the same way but without a supervised exercise class. Additionally, a step counter (Yamax Digi-Walker SW200 pedometer, Yamasa Tokei Keiki, Tokyo, Japan[26]) was used to motivate patients and their partners in both hospital and general practice. The total physical activity prescription was used to equip families with the necessary knowledge and skills to achieve and maintain the physical activity target safely in the community and during the long term.

For the **personal record card and family support pack** see http://www.escardio.org/euroaction

Nurses monitored the blood pressure and concentrations of cholesterol and glucose in all patients, and reviewed the results with physicians who treated the patients appropriately to achieve targets that were less than the 1998 European targets (panel). Patients with newly diagnosed diabetes mellitus were referred to diabetes specialists. The nurses educated families about their drugs to improve compliance.

In the hospitals, nurses coordinated a rolling programme of eight workshops—one a week—for coronary heart disease; cardiovascular risks—ie, lifestyle and risk factor control; cardioprotective medications; and return to work and leisure. In the general-practice centres, the workshop programme focused on lifestyle and risk factors.

On completion of the 16-week hospital programme, patients and their partners were reassessed for lifestyle, risk factors, and therapeutic management; results were sent to each individual's own family doctor. All identified patients—with coronary heart disease or at high risk—and their partners were invited back for reassessment at 1 year.

Laboratory analyses

Central laboratory analysis of total cholesterol, HDL cholesterol, triglycerides, glucose, and haemoglobin A_{1c} concentrations was undertaken at baseline, 16 weeks (hospital only), and 1 year. Serum concentrations of cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic colourimetric tests with Roche

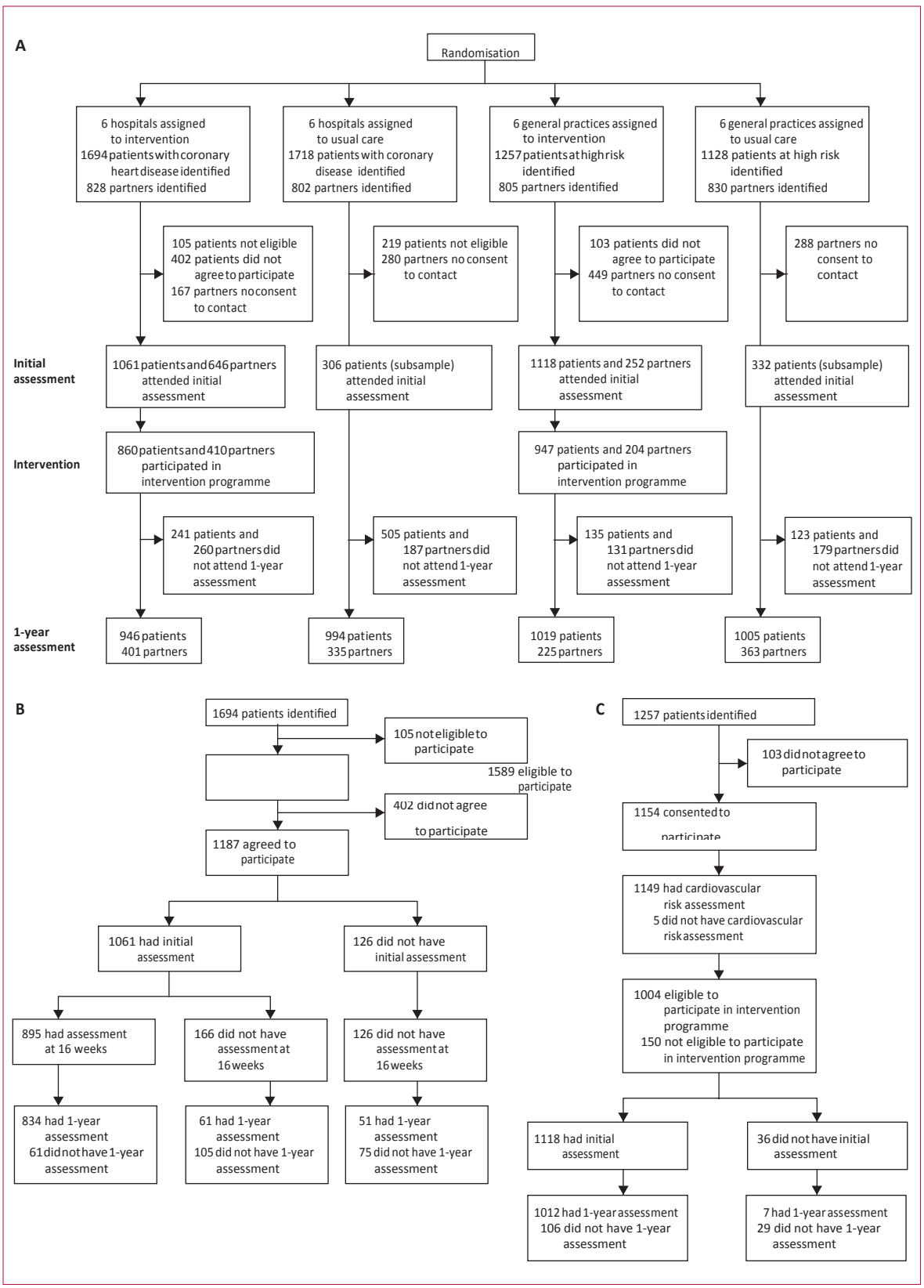

Figure 1: **Trial profile (A) and profiles of patients assigned to the hospital (B) and general-practice (C) intervention programmes**

liquid reagent assays (Roche Diagnostics, Basel, Switzerland) on a Roche 917 analyser (Roche Diagnostics). Plasma glucose concentrations were measured from fluoride oxalate samples with the hexokinase method on a Bayer Advia 1650 analyser (Bayer Diagnostics, Tarrytown, NY, USA). Haemoglobin A_{1c} was measured with the Multigent test on an Abbott Architect 8200 analyser (Abbott Diagnostics, Chicago, MI, USA). Between-batch coefficient of variation was less than 3·0% for cholesterol, 1·8% for glucose, and 1·5% for haemoglobin A_{1c}.

Statistical methods

The main statistical analysis based on intention to treat for prespecified primary endpoints (panel) was at a European level.[7] Six intervention hospitals were compared with six usual-care hospitals, and six intervention general practices were compared with six usual-care practices at 1 year with random-effects modelling. Additionally, post-hoc analyses of changes during the time between the initial and 1-year assessments are also reported, together with risk factor distributions. The results are reported according to CONSORT.[27]

For sample size calculations, the EUROASPIRE II study[4] was used to estimate the coefficients of variation for sample means and proportions. A sample size of 400 patients in both intervention and usual-care centres in each country was sufficient for detection of a 10% reduction in smoking, a 5% average reduction in bodyweight or systolic blood pressure, and a 10% reduction in mean total cholesterol concentration at the p=0·05 significance level with 80% power. The cluster coefficient for smoking was 0·200, bodyweight 0·011, systolic blood pressure 0·030, and total cholesterol concentration 0·062.[28]

Means and SDs were used to describe the continuous variables; frequencies and percentages were used to describe categorical variables. To account for clustering, the primary endpoints were analysed with random-effects modelling (with restricted maximum likelihood estimation) using SAS PROC MIXED (version 9.1.3) for continuous outcomes and SAS GLIMMIX (version 9.1.3) for binary outcomes. For the ordered categorical outcomes, proportional odds models were fitted within each country and the results combined with a random-effects meta-analysis. The results were not adjusted for multiple statistical testing. In a random subsample of usual-care patients, baseline measurements were taken so that a post-hoc comparison of change from baseline to 1-year between intervention and usual-care groups was possible. All identified patients and partners attending the 1 year reassessment were included in the statistical analyses (figure 1).

This trial is registered as ISRCTN 71715857.

Role of the funding source

The sponsor had no role in the design, data collection, data analysis, data interpretation, and writing of this report. The authors and the steering committee had full access to all data and had final responsibility for the decision to submit for publication.

Results

Table 1 shows patients and their partners' demographics, participation, and 1-year assessments in hospital and general-practice centres. Table 2 shows the results of the initial assessments and the proportions of patients and their partners achieving lifestyle, risk factor, and drug targets for cardiovascular disease prevention. Figure 1 shows the trial profile.

Among patients with coronary heart disease who reported smoking in the month before their cardiac event, a higher proportion in the intervention group were not smokers (validated breath carbon monoxide concentration <6 parts per million) at 1 year compared with the usual-care group (table 3; figure 2). The proportion of non-smoking high-risk patients in the intervention and usual-care groups did not differ (table 3). Non-smoking at 1 year was greater, although not significantly so, in the partners of patients in the intervention groups than in usual-care groups (table 3).

A higher proportion of patients with the coronary heart disease in the intervention group attained the dietary targets for saturated fat intake (subsample), fruit and vegetables, and oily fish at 1 year than the proportion of patients in the usual-care group (table 3). Similar differences were noted for high-risk patients in the intervention and usual-care groups, although the differences were only significant for fruit and vegetables (table 3).

The proportions of patients with coronary heart disease (ie, in hospital) attaining these dietary targets increased between the initial and 1-year assessments in both the intervention and usual-care groups, but the increase was greater in the intervention group than in the usual-care group for fruit and vegetables (difference in change 15·8%, 95% CI 2·2 to 29·3, p=0·03) and oily fish consumption (11·4%, 0·6 to 22·1, p=0·04). The increase was in favour of the intervention for saturated fat intake (11·2%, −16·1 to 38·4, p=0·34) and fish consumption (11·8%, −2·1 to 25·6, p=0·08). A similar pattern was noted for high-risk patients (ie, in general practice) with a change from baseline that was greater in the intervention group than in the usual-care group for fruit and vegetables (23·6%, 9·1 to 38·2, p=0·009). The increase was in favour of the intervention for fish consumption (16·5%, −0·1 to 33·1%, p=0·051) and oily fish consumption (2·2%, −1·7 to 6·2%, p=0·20). For partners of both groups of patients, the proportions achieving dietary targets were generally greater in the intervention groups than in the usual-care groups for all targets, although only significant for fruit and vegetables (table 3).

The proportions of patients with coronary heart disease and those at high risk achieving the target for self-reported physical activity at 1 year were significantly higher in the

	Hospital		General practice					
	Coronary patients		Partners		High-risk patients		Partners	
	INT	UC	INT	UC	INT	UC	INT	UC
Identified	1694	1718	828	802	1257	1128	805	830
Eligible	1589 (94%)	1499 (87%)	661 (80%)*	522 (65%)*	1189 (95%)	n/a	356 (44%)*	542 (65%)*
Initial assessment	1061 (67%)	306 (20%)†	646 (98%)	n/a	1118 (94%)	332 (29%)†	252 (71%)	n/a
Participation in EUROACTION	860 (81%)‡	n/a	410 (63%)‡	n/a	947 (85%)§	n/a	204 (81%)§	n/a
1–year assessment	946 (60%)	994 (66%)	401 (61%)	335 (64%)	1019 (86%)	1005 (89%)	225 (63%)	363 (67%)
Age group								
<55 years	210 (22%)	221 (22%)	92 (23%)	84 (25%)	226 (22%)	149 (15%)	42 (19%)	64 (18%)
55–64 years	334 (35%)	340 (34%)	154 (38%)	138 (41%)	447 (44%)	486 (48%)	112 (50%)	177 (49%)
≥65 years	402 (42%)	433 (44%)	152 (38%)	112 (33%)	346 (34%)	370 (37%)	71 (32%)	122 (34%)
Age (years)	62·5 (9·9)	63·0 (9·6)	61·6 (10·3)	60·7 (9·8)	62·0 (7·6)	62·8 (7·3)	61·8 (7·0)	62·0 (7·2)
Men	666 (70%)	695 (70%)	84 (21%)	71 (21%)	507 (50%)	577 (57%)	77 (34%)	120 (33%)
Diagnostic category								
AMI¶/HeartScore ≥5%||	451 (47%)	533 (54%)	n/a	n/a	431 (42%)	511 (51)	n/a	n/a
Unstable angina¶/BP-lipids||	156 (16%)	210 (21%)	n/a	n/a	272 (27%)	230 (23%)	n/a	n/a
Stable angina¶/diabetes||	339 (36%)	251 (25%)	n/a	n/a	316 (31%)	264 (26%)	n/a	n/a

Data are number, number (%), or mean (SD). INT=intervention. UC=usual care. n/a=not applicable. AMI=acute myocardial infarction. BP-lipids=patients on antihypertensive or lipid-lowering treatments. *Consent given by patients for their partners to be contacted. †Random subsample only. ‡Reported at 16 weeks as a proportion of patients at the initial assessment. §Reported at 1 year as a proportion of initial assessment. ¶Hospital group. ||General-practice group.

Table 1: **Patient and partner demographics**

intervention groups than in the usual-care groups (table 3). The proportion of patients with coronary heart disease achieving this target in the intervention group increased by 26·8% between the initial and 1-year assessments, compared with 0·8% in the usual-care subsample; the difference in change was 28·0% (95% CI 4·1 to 51·8, p=0·03). The proportion of high-risk patients achieving this target increased by 23·5% in the intervention group compared with a reduction of 10·2% in the usual-care subsample; the difference in change was 32·9% (11·8 to 53·9, p=0·01). Similar differences between the intervention and usual-care groups were noted among the partners of both groups of patients, although the proportions achieving their targets tended to be lower among partners than in patients (table 3).

Proportions of patients with coronary heart disease and those at high risk attaining the ideal BMI at 1 year, and the distribution of BMI, showed no significant differences between the intervention and usual-care groups (table 3; table 4).

However, for those coronary and high-risk patients with a BMI of 25 kg/m^2 or more at initial assessment, the proportions attaining ideal BMI (ie, <25 kg/m^2) at 1 year were higher in the intervention group than in the usual-care subsample but not significantly so. In patients with coronary heart disease, the mean BMI change from baseline was −0·27 kg/m^2 in the intervention group compared with 0·44 kg/m^2 in the usual-care subsample; the difference in change was −0·69 kg/m^2 (95% CI −1·03 to −0·34, p=0·004). Mean BMI change for high-risk patients was −0·47 kg/m^2 in the intervention group compared with 0·13 kg/m^2 in the usual-care subsample, resulting in a difference in change of −0·56 kg/m^2 (−0·86 to −0·25, p=0·005). In those with a BMI of 25 kg/m^2 or more at initial assessment, proportions of individuals achieving weight loss of at least 5% at 1 year were higher for both groups of patients—ie, coronary heart disease and high risk—in the intervention groups than for patients in the usual-care groups, but significant only for the high-risk patients (table 3). Changes during the initial to 1-year assessments were reductions in mean weight in the intervention groups and increases in the mean weight in the usual-care subsample. The difference in weight change was −1·56 kg (−3·0 to −0·1, p=0·04) for patients with coronary heart disease and −1·51 kg (−2·53 to −0·50, p=0·01) for high-risk patients. The proportion of partners attaining ideal BMI target at 1 year did not differ between the intervention and usual-care groups (table 3). Partners were not screened in the usual-care group at baseline.

Proportions of patients with coronary heart disease and those at high risk of cardiovascular disease achieving ideal waist circumference at 1 year was slightly higher, though not significant, in the intervention groups than in the usual-care groups (table 3). However, comparison of the distributions of waist circumference between intervention and usual-care groups for both groups of patients favoured intervention (table 4).

For patients with coronary heart disease and a waist circumference greater than the target at initial assessment, the proportion of individuals attaining the

	Hospital			General practice		
	Coronary patients		Partners*	High-risk patients		Partners*
	INT	UC	INT	INT	UC	INT
Initial assessment	1061	306	646	1118	332	252
Not smoking (breath carbon monoxide <6 parts per million)	933/1058 (88%)	256/302 (85%)	521/643 (81%)	761/1110 (69%)	225/328 (69%)	200/244 (82%)
Saturated fat (<10% of total energy)†	64/148 (43%)	38/107 (36%)	37/83 (45%)	..	..	..
Oily fish (≥3 times per week)	33/1060 (3%)	15/304 (5%)	15/640 (2%)	55/1094 (5%)	10/331 (3%)	27/245 (11%)
Fish (≥20 g per day)	589/1060 (56%)	178/304 (59%)	373/640 (58%)	680/1096 (62%)	217/331 (66%)	159/245 (65%)
Fruit and vegetables (≥400 g per day)	480/1060 (45%)	85/304 (28%)	325/640 (51%)	548/1093 (50%)	117/331 (35%)	131/245 (53%)
Physical activity (≥30 min, ≥4 times per week)	273/1056 (26%)	74/304 (24%)	169/635 (27%)	313/1080 (29%)	107/331 (32%)	74/245 (30%)
Body-mass index (<25 kg/m^2)	229/1057 (22%)	71/303 (23%)	225/634 (35%)	209/1094 (19%)	61/331 (18%)	63/243 (26%)
Ideal waist circumference (men <94 cm; women <80 cm)	272/1056 (26%)	84/299 (28%)	192/632 (30%)	212/1087 (20%)	56/331 (17%)	50/241 (21%)
Blood pressure (<140/90 mm Hg or <130/85 mm Hg in individuals with diabetes)	680/1061 (64%)	200/304 (66%)	370/645 (57%)	406/1103 (37%)	125/331 (38%)	140/244 (57%)
Total cholesterol (<5 mmol/L)	700/951 (74%)	190/274 (69%)	61/167 (37%)	250/1089 (23%)	96/306 (31%)	25/81 (31%)
LDL cholesterol (<3 mmol/L)	695/930 (75%)	186/267 (70%)	69/165 (42%)	296/1053 (28%)	108/295 (37%)	28/78 (36%)
Haemoglobin A_{1c} (<7% in individuals with diabetes)	66/141 (47%)	15/36 (42%)	9/15 (60%)	234/327 (72%)	63/88 (72%)	‡
Antiplatelet drugs	1001/1061 (94%)	290/305 (95%)	58/643 (9%)	86/1118 (8%)	30/332 (9%)	28/246 (11%)
β blockers	828/1061 (78%)	259/305 (85%)	81/643 (13%)	147/1118 (13%)	40/332 (12%)	38/246 (15%)
Angiotensin-converting enzyme inhibitors	586/1061 (55%)	143/305 (47%)	72/643 (11%)	217/1113 (19%)	53/330 (16%)	29/246 (12%)
Statins	832/1059 (79%)	240/303 (79%)	62/643 (10%)	166/1118 (15%)	59/332 (18%)	29/246 (12%)

Data are number or n/N (%). INT=intervention. UC=usual care. *No initial assessment in the usual-care group. †Random subsample only. ‡Only two partners with self-reported diabetes had a haemoglobin A_{1c} measurement.

Table 2: **Coronary heart disease and high-risk patients and their partners achieving the primary endpoints at the initial assessment**

target at 1 year was 88/665 (13%) in the intervention group and 15/169 (9%) in the usual-care subsample, which was a difference of 5·8% (95% CI −0·9 to 12·5, p=0·08). Mean change in waist circumference from baseline for the same patients was −1·5 cm in the intervention group and −0·8 cm in the usual-care subsample—ie, a difference in change of −0·8 cm (−3·7 to 2·1, p=0·51). For high-risk patients in general practice with a waist circumference greater than the target at initial assessment, 58/798 (7%) achieved the target at 1 year in the intervention group and 8/195 (4%) in the usual-care subsample—ie, a difference of 3·2% (−1·5 to 7·9, p=0·19). Mean change in waist circumference from baseline was −1·66 cm in the intervention group and −0·21 cm in the usual-care subsample, which resulted in a difference of −1·61 cm (−2·61 to −0·61, p=0·009). The proportions of partners (of both coronary patients and high-risk individuals) achieving target waist circumference at 1 year were slightly higher in the intervention groups than in the usual-care groups, though the differences were not significant (table 3).

A higher proportion of coronary patients in the intervention group achieved the blood pressure target at 1 year than that in the usual-care group (table 3). Comparison of the distribution of systolic blood pressure between the intervention and usual-care groups in patients with coronary heart disease favoured intervention, but diastolic blood pressure was not different (table 4). Mean change in systolic blood pressure from baseline was 0·6 mm Hg in the intervention group compared with 4·2 mm Hg in the usual-care subsample—ie, a difference in change of −4·3 mm Hg (95% CI −10·4 to 1·8, p=0·13). Mean change in diastolic blood pressure was −0·5 mm Hg in the intervention group and 1·1 mm Hg in the usual-care subsample—ie, a difference in change of −2·2 mm Hg (−6·0 to 1·7, p=0·20). Of the patients with coronary heart disease and a blood pressure greater than the target level or those on antihypertensive medications, or both, 576/903 (64%) were treated and achieved the target goal for blood pressure; 311/903 (34%) were treated but not at the target goal; and 16/903 (2%) were not treated and not at the target goal in the intervention group compared with 522/962 (54%), 413/962 (43%), and 27/962 (3%), respectively, in the usual-care group (odds ratio [OR] 0·65, 0·42 to 1·01, p=0·05). The difference in the proportion treated and achieving the target goal at 1 year in the intervention group versus the usual-care group was 9·9% (−0·2 to 20·0, p=0·05).

A higher proportion of high-risk patients achieved the blood pressure target at 1 year in the intervention group than in the usual-care group (table 3). Comparison of the distributions of both systolic and diastolic blood pressures in high-risk patients favoured the intervention group (table 4). Mean change in systolic blood pressure between the initial and 1-year assessments was −7·6 mm Hg in the intervention group compared with −2·8 mm Hg in the usual-care subsample, a difference in change from baseline of −4·8 mm Hg (95% CI −10·2 to 0·6, p=0·07). Mean change for diastolic blood pressure was −4·1 mm Hg in the intervention group and −1·6 mm Hg in the usual-care group, a difference in change from baseline of −2·7 mm Hg (−5·9 to 0·6, p=0·09). Of the high-risk patients with a blood pressure greater than the target level or those on antihypertensive medications, or both, 297/722 (41%) were treated and at their target goal for blood pressure; 270/722 (37%) were treated but not at the target goal; and 155/722 (21%) were not treated and not at the target goal in the intervention group versus 156/755 (21%), 288/753 (38%), and 309/753 (41%), respectively, in the usual-care group (OR 0·37, 0·22 to 0·63, p=0·005). The difference in the proportion treated and achieving the target goal at 1 year in the intervention group versus the usual-care group was 20·3% (4·6 to 36·1, p=0·02).

The proportions of patients with coronary heart disease achieving their targets for both total and LDL-cholesterol concentrations at 1 year were slightly higher in the intervention group than in the usual-care group, though not significant (table 3); differences in distributions were not significant (table 4). The mean changes from baseline in concentrations of total and LDL cholesterol in the intervention and the usual-care groups were very small. Among the patients with coronary heart disease and total cholesterol concentrations greater than the target concentrations or those on lipid-lowering medication, or both, 618/811 (76%) were treated and at the target goal; 144/811 (18%) were treated but not at the target goal; and 49/811 (6%) were not treated and not at the target goal in

	Hospital						General practice					
	Coronary patients			Partners			High-risk patients			Partners		
	INT	UC	Difference	INT	UC	Difference	INT	UC	Difference	INT	UC	Difference
1-year assessment	946	994	n/a	401	335	n/a	1019	1005	n/a	225	363	n/a
Not smoking*	136/235 (58%)	154/327 (47%)	10·4% (−0·3 to 21·2); p=0·06	21/65 (32%)	10/57 (18%)	14·9% (−7·2 to 36·9); p=0·13	740/1007 (73%)	712/985 (72%)	0·8% (−13·1 to 14·7); p=0·89	187/220 (85%)	281/354 (79%)	7·6% (−0·6 to 15·8); p=0·07
Saturated fat (<10% of total energy)†	196/356 (55%)	168/417 (40%)	17·3% (6·4 to 28·2); p=0·009	96/160 (60%)	45/107 (42%)	13·5% (−24·0 to 51·3); p=0·31	..	..	..	..	..	..
Oily fish (≥3 times per week)	156/944 (17%)	81/994 (8%)	8·9% (0·3 to 17·5); p=0·04	42/397 (11%)	25/335 (7%)	1·3% (−7·2 to 9·8); p=0·71	113/1019 (11%)	60/1004 (6%)	6·7% (−4·1 to 17·6); p=0·13	44/225 (20%)	25/363 (7%)	11·1% (−0·3 to 22·5); p=0·054
Fish (≥20 g per day)	746/944 (79%)	665/994 (67%)	8·7% (−33·3 to 50·6); p=0·62	309/397 (78%)	212/334 (63%)	6·7% (−32·7 to 46·1); p=0·68	841/1018 (83%)	666/1003 (66%)	16·8% (−1·7 to 35·2); p=0·07	182/225 (81%)	238/363 (66%)	13·2% (−13·6 to 40·1); p=0·26
Fruit and vegetables (≥400 g per day)	680/944 (72%)	349/991 (35·%)	37·3% (18·1 to 56·5); p=0·004	286/397 (72%)	122/334 (37%)	34·5% (18·2 to 50·7); p=0·002	799/1019 (78%)	388/1001 (39%)	39·7% (18·1 to 61·3); p=0·005	173/225 (77%)	196/363 (54%)	25·1% (14·5 to 35·7); p=0·002
Physical activity (≥30 min, ≥4 times per week)	507/942 (54%)	194/992 (20%)	35·6% (20·0 to 51·3); p=0·002	163/400 (41%)	89/335 (27%)	18·7% (−0·6 to 379); p=0·06	512/1018 (50%)	222/1003 (22%)	29·4% (10·7 to 48·0); p=0·01	100/225 (44%)	89/362 (25%)	26·8% (4·1 to 49·6); p=0·03
BMI (<25 kg/m^2)	257/945 (27%)	205/990 (21%)	5·3% (−3·8 to 14·4); p=0·20	147/384 (38%)	113/334 (34%)	7·1% (−7·2 to 21·3); p=0·26	230/1018 (23%)	220/1002 (22%)	0·6% (−6·9 to 8·0); p=0·85	65/222 (29%)	117/362 (32%)	−2·8% (−13·1 to 7·5); p=0·52
Weight loss (≥5% in patients with BMI ≥25 kg/m^2 at initial assessment)	135/695 (19%)	24/183 (13%)	6·2% (−7·1 to 19·5); p=0·28	..	..	..	134/814 (16%)	13/192 (7%)	10·4% (4·7 to 16·1); p=0·005	..	..	..
Ideal waist circumference (men <94 cm; women <80 cm)	292/945 (31%)	213/991 (21%)	8·7% (−2·7 to 20·3); p=0·11	107/384 (28·%)	86/334 (26%)	7·4% (−3·6 to 18·4); p=0·10	234/1009 (23%)	152/1001 (15%)	7·9% (−2·3 to 18·1); p=0·10	60/221 (27%)	89/361 (25%)	4·7% (−9·9 to 19·2); p=0·45
Blood pressure (<140/90 mm Hg; <130/85 mm Hg in patients with diabetes)	615/942 (65%)	547/990 (55%)	10·4% (0·6 to 20·2); p=0·04	266/397 (67%)	211/335 (63%)	8·0% (−8·2 to 24·2); p=0·21	586/1016 (58%)	407/1004 (41%)	16·9% (2·0 to 31·8); p=0·03	158/222 (71%)	193/363 (53%)	21·7 (2·8 to 40·7); p=0·03
Blood pressure (<140/90 mm Hg in patients without diabetes)	553/769 (72%)	490/816 (60%)	11·9% (1·2 to 22·6); p=0·04	..	..	..	459/687 (677)	356/735 (48%)	16·6% (0·5 to 32·8); p=0·04	..	..	..

(Continues on next page)

	Hospital						General practice					
	Coronary patients			Partners			High-risk patients			Partners		
	INT	UC	Difference	INT	UC	Difference	INT	UC	Difference	INT	UC	Difference
(Continued from previous page)												
Blood pressure (<130/85 mm Hg in patients with diabetes)	63/174 (36%)	57/174 (33%)	6·3% (–6·6 to 19·2); p=0·26	..	..	..	127/329 (39%)	51/269 (19%)	18·8% (0·9 to 36·7); p=0·04	..	..	..
Total cholesterol (<5 mmol/L)	664/857 (77%)	621/877 (71%)	6·6% (–5·8 to 19·0); p=0·23	85/245 (35%)	100/303 (33%)	3·0% (–48·7 to 54·7); p=0·60	345/965 (36%)	295/937 (31%)	2·4% (–9·9 to 14·8); p=0·64	68/205 (33%)	101/334 (30%)	1·7% (–2·9 to 16·3); p=0·76
LDL cholesterol (<3 mmol/L)	673/834 (81%)	633/856 (74%)	7·3% (0·9 to 15·4); p=0·07	105/245 (43%)	118/294 (40%)	4·5% (–50·0 to 59·0); p=0·48	419/936 (45%)	320/908 (35%)	8·7% (–5·2 to 22·7); p=0·17	80/203 (39%)	124/331 (37%)	2·3% (13·9 to 18·6); p=0·71
Haemoglobin A_{1c} (<7% in individuals with diabetes)	90/160 (56%)	77/144 (53%)	10·8% (–12·9 to 34·5); p=0·29	..	..	..	246/308 (80%)	155/237 (65%)	12·1% (–4·7 to 29·0); p=0·12	..	..	..
Antiplatelet drugs	881/945 (93%)	914/991 (92%)	1·6% (–1·8 to 5·1); p=0·28	54/399 (14%)	48/334 (14%)	–3·2% (–13·2 to 6·8); p=0·45	136/1012 (13%)	102/1004 (10%)	3·9% (–2·7 to 10·5); p=0·19	32/222 (14%)	33/363 (9%)	2·2% (–3·3 to 7·8); p=0·35
β blockers	722/945 (76%)	794/991 (80%)	–3·1% (–7·9 to 1·7); p=0·16	68/399 (17%)	57/334 (17%)	–1·2% (–12·0 to 9·6); p=0·79	176/1012 (17%)	158/1004 (16%)	–0·4% (–8·4 to 7·7); p=0·91	42/222 (19%)	45/363 (12%)	4·4% (–8·9 to 17·8); p=0·43
Angiotensin-converting enzyme inhibitors	495/945 (52%)	557/991 (56%)	–5·5% (–16·6 to 5·7); p=0·26	65/399 (16%)	35/334 (10%)	0·4% (–8·4 to 9·1); p=0·92	297/1012 (29%)	196/1004 (20%)	8·5% (1·8 to 15·2); p=0·02	27/222 (12)	40/363 (11%)	0·5% (–5·4 to 6·4); p=0·84
Statins	810/945 (86%)	794/991 (80%)	6·0% (–0·5 to 11·5); p=0·04	76/399 (19%)	50/334 (15%)	4·0% (–6·7 to 14·8); p=0·38	381/1012 (38%)	232/1004 (23%)	14·6% (2·5 to 26·7); p=0·03	49/222 (22%)	56/363 (15%)	7·2% (–6·2 to 20·7); p=0·23

Data are number, n/N (%), or difference between intervention and usual-care groups (95% CI). The difference in percentages were calculated by combining the country-specific differences using a random-effects meta-analysis. INT=intervention. UC=usual care. BMI=body-mass index. n/a=not applicable. *Hospital patients achieving the target goal as a proportion of the target population (self-reported smoking in the month before the index event); proportion of patients in general practice not smoking at final assessment. †Random subsample only.

Table 3: **Coronary heart disease and high-risk patients and their partners achieving the primary endpoints at 1 year**

the intervention group compared with 572/829 (69%), 152/829 (18%), and 105/829 (13%), respectively, in the usual-care group (OR 0·68, 95% CI 0·31 to 1·45, p=0·24). The difference between the intervention and usual-care groups in the proportion of patients treated and achieving the target goal was 7·4% (–5·8 to 207·0, p=0·21). For LDL-cholesterol concentration, 625/786 (80%) of patients with coronary heart disease were treated and at the target goal; 117/786 (15%) were treated but not at the target goal; and 44/786 (6%) were not treated and not at the target goal in the intervention group compared with 577/800 (72%), 129/800 (16%), and 94/800 (12%), respectively, in the usual-care group (OR 0·60, 0·35 to 1·02, p=0·06). The difference between the two groups in the proportion of patients treated and achieving the target goal was 8·1% (–1·0 to 17·2, p=0·07).

The proportions of individuals at high risk of cardiovascular disease achieving lipid targets at 1 year were substantially lower than those of patients with coronary heart disease, and the differences between the intervention and usual-care groups at 1 year were not significant (table 3), and the distribution of lipids was not significant (table 4). However, a considerably smaller proportion of patients achieved the total cholesterol target concentration at baseline in the intervention group (228/1000 [23%]) than in the usual-care subsample (72/221 [32%]) and mean concentration of total cholesterol was higher in the intervention group than in the usual-care group (5·7 mmol/L *vs* 5·5 mmol/L,

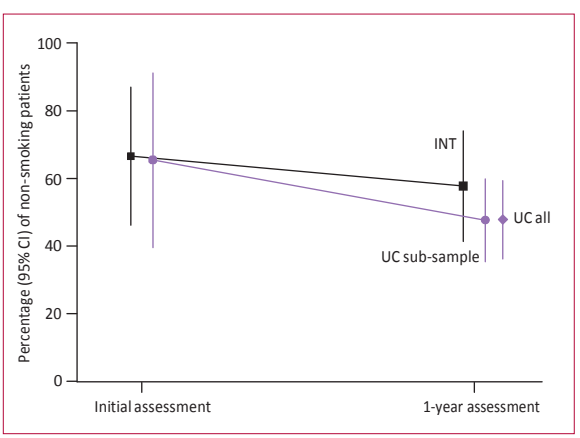

Figure 2: **Proportion of non-smoking patients at the initial and 1-year assessments among those reported as smoking in the month before the index event**

Error bars represent 95% CI. INT=intervention. UC=usual care.

p=0·002). In the intervention group, the proportion of patients achieving the total cholesterol target concentration increased compared with a reduction in the usual-care group, a difference in change of 12·7% (95% CI 2·4 to 23·0, p=0·025; figure 3). For LDL cholesterol, the proportion attaining the target concentration increased in the intervention group compared with no change in usual-care group, a difference in change of 16·7% (6·7 to 26·7, p=0·008; figure 3). The mean change in the concentration of total

cholesterol between the initial and 1-year assessments was −0·38 mmol/L in the intervention group compared with no change in the usual-care subsample, a difference in change from baseline of −0·34 mmol/L (−0·54 to −0·15, p=0·006). For LDL-cholesterol concentration, the change from baseline was −0·41 mmol/L in the intervention group versus −0·03 in the usual-care subsample, a difference in change of −0·34 mmol/L (−0·52 to −0·16, p=0·004).

Self-reported diabetes in patients with coronary heart disease at 1 year was the same in the intervention (174/946 [18%]) and usual-care groups (176/994 [18%]), and was 331/1019 (32%) for high-risk patients in the intervention group versus 269/1004 (27%) in the usual-care group, a difference of 5·1% (95% CI −11·4 to 21·7, p=0·46). Proportions of patients—with coronary heart disease and at high risk—with controlled diabetes (haemoglobin A_{1c} <7%) were higher in the intervention groups than in the usual-care groups, but the differences were not significant (table 3). Comparison of the distributions of fasting blood glucose concentrations between the two groups for patients with coronary heart disease and diabetes favoured intervention, but for the high-risk patients with diabetes the difference was not significant. No significant differences were noted for either group of patients in the distribution of haemoglobin A_{1c} (table 4). In patients with coronary heart disease, the mean fasting blood glucose concentration decreased by 0·07 mmol/L in the intervention group compared with a reduction of 0·15 mmol/L in the usual-care group, a difference in change of 0·06 mmol/L (−0·43 to 0·55, p=0·76). In high-risk patients the reductions were −0·46 mmol/L in the intervention group and −0·28 mmol/L in the usual-care group, a difference in change of −0·11 mmol/L (−0·75 to 0·53, p=0·67).

In patients with coronary heart disease treated with cardioprotective drugs, significant differences between the intervention and usual-care groups were noted only for statins (table 3), which were prescribed more frequently in the intervention group. In general practice, patients in the intervention group had more prescriptions for angiotensin-converting enzyme inhibitors and statins than did patients in the usual-care group (table 3). Overall, the use of cardioprotective drugs was much less

	Hospital				General practice			
	Intervention	Usual care	Odds ratio (95% CI)	p value	Intervention	Usual care	Odds ratio (95% CI)	p value
Body-mass index			0·77 (0·49–1·21)	0·20			1·14 (0·83–1·58)	0·34
<25 kg/m²	257/945 (27%)	205/990 (21%)			230/1018 (23%)	220/1002 (22%)		
25–29 kg/m²	436/945 (46%)	473/990 (48%)			433/1018 (43%)	490/1002 (49%)		
≥30 kg/m²	252/945 (27%)	312/990 (32%)			355/1018 (35%)	291/1002 (29%)		
Waist circumference			0·61 (0·39–0·97)	0·04			0·70 (0·53–0·93)	0·02
<94 cm (men); <80 cm (women)	292/945 (31%)	213/990 (22%)			234/1009 (23%)	152/1001 (15%)		
94–101 cm (men); 80–87 cm (women)	274/945 (29%)	256/990 (26%)			256/1009 (25%)	265/1001 (26%)		
≥102 cm (men); ≥88 cm (women)	379/945 (40%)	521/990 (53%)			519/1009 (51%)	584/1001 (58%)		
Systolic blood pressure			0·58 (0·38–0·88)	0·02			0·39 (0·23–0·65)	0·005
<140 mm Hg	672/942 (71%)	603/990 (61%)			728/1016 (72%)	611/1004 (61%)		
140–159 mm Hg	200/942 (21%)	247/990 (25%)			231/1016 23%)	250/1004 (25%)		
≥160 mm Hg	70/942 (7%)	141/990 (14%)			57/1016 (6%)	143/1004 (14%)		
Diastolic blood pressure			0·48 (0·18–1·28)	0·11			0·46 (0·26–0·81)	0·016
<90 mm Hg	848/942 (90%)	830/990 (84%)			875/1016(86%)	749/1004 (75%)		
90–99 mm Hg	69/942 (7%)	122/990 (12%)			116/1016 (11%)	196/1004 (20%)		
≥100 mm Hg	25/942 (3%)	38/990 (4%)			25/1016 (2%)	59/1004 (6%)		
Total cholesterol			0·78 (0·42–1·45)	0·34			0·84 (0·52–1·37)	0·41
<4 mmol/L	308/857 (36%)	295/880 (34%)			72/965 (7%)	64/937 (7%)		
4–4·9 mmol/L	356/857 (42%)	328/880 (37%)			273/965 (28%)	232/937 (25%)		
5–5·9 mmol/L	147/857 (17%)	173/880 (20%)			391/965 (41%)	368/937 (39%)		
≥6 mmol/L	(46/857 (5%)	84/880 (10%)			229/965 (24%)	273/937 (29%)		
LDL cholesterol			0·74 (0·46–1·17)	0·15			0·67 (0·40–1·13)	0·11
<2 mmol/L	270/834 (32%)	251/856 (29%)			94/936 (10%)	67/908 (7%)		
2–2·9 mmol/L	403/834 (48%)	382/856 (45%)			325/936 (35%)	254/908 (28%)		
3–3·9 mmol/L	126/834 (15%)	170/856 (20%)			377/936 (40%)	387/908 (43%)		
≥4 mmol/L	35/834 (4%)	53/856 (6%)			140/936 (15%)	200/908 (22%)		

(Continues on next page)

	Hospital				General practice			
	Intervention	Usual care	Odds ratio (95% CI)	p value	Intervention	Usual care	Odds ratio (95% CI)	p value
(Continued from previous page)								
Fasting blood glucose			0·83 (0·36–1·91)	0·58			0·67 (0·33–1·36)	0·21
≤6 mmol/L	508/688 (74%)	496/720 (69%)			549/643 (85%)	524/659 (80%)		
6·1–6·9 mmol/L	133/688 (19%)	150/720 (21%)			71/643 (11%)	97/659 (15%)		
7–7·9 mmol/L	38/688 (6%)	50/720 (7%)			18/643 (3%)	26/659 (4%)		
≥8 mmol/L	9/688 (1%)	24/720 (3%)			5/643 (<1%)	12/659 (2%)		
Fasting blood glucose (patients with diabetes)			0·43 (0·19–0·99)	0·048			0·50 (0·17–1·50)	0·17
≤6 mmol/L	34/159 (21%)	13/149 (9%)			89/305 (29%)	50/232 (22%)		
6·1–6·9 mmol/L	27/159 (17%)	21/149 (14%)			105/305 (34%)	53/232 (23%)		
7–7·9 mmol/L	36/159 (23%)	26/149 (17%)			54/305 (18%)	57/232 (25%)		
≥8 mmol/L	62/159 (39%)	89/149 (60%)			57/305 (19%)	72/232 (31%)		
Haemoglobin A_{1c} (patients with diabetes)			0·51 (0·20–1·32)	0·13			0·56 (0·22–1·41)	0·17
≤6%	58/160 (36%)	33/154 (21%)			131/308 (43%)	59/237 (25%)		
6–6·9%	39/160 (24%)	44/154 (29%)			115/308 (37%)	96/237 (41%)		
7–7·9%	36/160 (23%)	31/154 (20%)			36/308 (12%)	47/237 (20%)		
≥8%	27/160 (17%)	46/154 (30%)			26/308 (8%)	35/237 (15%)		

Data are n/N (%), unless otherwise indicated.

Table 4: **Risk-factor distributions in coronary heart disease and high-risk patients**

in general practice than in hospitals. Prescription practice adhered to local policy and doctors in the EUROACTION programme tended to prescribe cheaper generic drugs.

Discussion

The EUROACTION preventive cardiology programme reduced the risk of cardiovascular disease compared with usual care mainly through lifestyle changes by families, who together made healthier food choices and became more physically active than before the intervention. This change led to some weight loss and, for high-risk patients, a reduction in central obesity. Blood pressure control was improved and for patients with coronary heart disease without the use of additional antihypertensive drugs. Control of blood cholesterol concentrations in these patients was improved in both the intervention and usual-care groups; improvement was significant in high-risk patients because of the increased use of statins. However, the use of all cardioprotective drugs was substantially lower in primary care than in the hospitals.

Although these results are encouraging there is scope for improvement. The smoking cessation intervention based on advice reduced relapse in patients with coronary heart disease but had no effect on the high-risk patients. Even though the protocol recommended the use of smoking cessation therapies, these were not used because of cost. Although the same protocol for risk-factor management was used in hospital and general practice, use of blood pressure and lipid-lowering drugs was much more conservative in general practice. As a consequence, most of the high-risk patients did not achieve lipid targets. Diabetes care could have been improved if the intervention nurses had taken responsibility for diabetes management.

Although, exercise-based cardiac rehabilitation reduces both cardiac and total mortality, the results of a meta-analysis showed no difference in mortality effect between exercise-only cardiac rehabilitation and comprehensive cardiac rehabilitation.[29] Importantly, the effect of cardiac rehabilitation on total mortality was independent of coronary heart disease diagnosis, type of cardiac rehabilitation, amount of exercise intervention, or duration of follow-up. The contribution of secondary prevention programmes with or without exercise was assessed in a separate meta-analysis.[30] The effects on mortality and myocardial infarction were similar for programmes that included both exercise and risk-factor education, risk-factor education alone, or exercise alone. In a systematic review of trials of secondary prevention, multidisciplinary disease management programmes reduced admissions to hospital and recurrent myocardial infarction.[31] However, this distinction between cardiac rehabilitation and secondary prevention is artificial and these meta-analyses showed the benefits of a comprehensive approach to reduction of total cardiovascular risk. The EUROACTION model took this comprehensive approach and addressed all aspects of lifestyle, risk factor management, and cardioprotective drug treatments, which is likely to have the greatest effect on cardiovascular morbidity and mortality.

In primary prevention, the evidence for multiple risk factor interventions is less strong. In a systematic review of ten trials with outcome data, no significant effect on

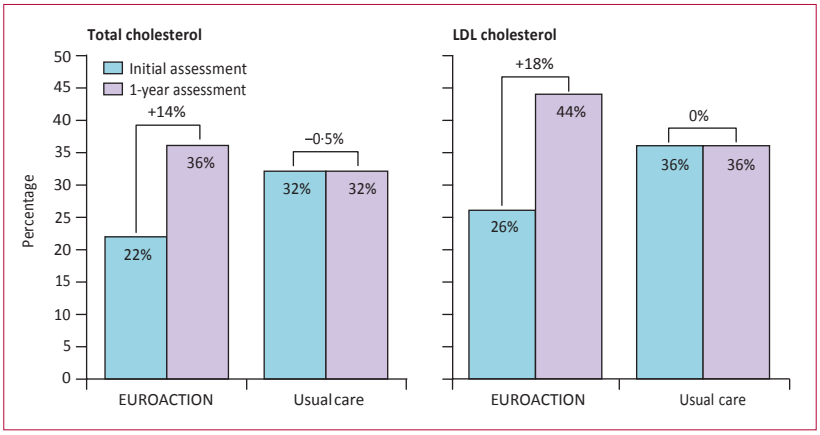

Figure 3: **Changes in proportions of high-risk patients achieving the European target for concentrations of lipids in intervention and usual-care subsamples between initial and 1-year assessments**
European target was less than 5 mmol/L for total cholesterol concentration and less than 3 mmol/L for LDL cholesterol.

total or coronary mortality was noted but a small and potentially important 10% reduction in coronary heart disease mortality might have been missed.[32] This apparent absence of effect on coronary mortality indicated a modest reduction in smoking and small changes (due to restricted drug treatment) in blood pressure and concentrations of lipids in these trials. By contrast, EUROACTION was more effective than usual care because a lifestyle intervention was combined with cardioprotective drugs that together reduced cardiovascular events.

The EUROACTION programme incorporated several important principles. It was intentionally set up in busy general hospitals and general practices, outside specialist cardiac rehabilitation centres, to provide a service for all coronary and high-risk patients in routine clinical practice. Integration of the diagnosis and management of patients with continued preventive care in the same medical facility is likely to result in increased and sustained participation. In the EUROASPIRE survey,[6] only a third of coronary patients attended cardiac rehabilitation, whereas two-thirds joined the EUROACTION programme. Recruitment was even better in primary care, with nine out of ten patients joining the programme. EUROACTION was inclusive because it addressed all the high-priority patient groups as defined in the guidelines.[7] We made no distinction between symptomatic coronary disease (secondary prevention) and those at high risk (primary prevention). All these patients are at high risk of cardiovascular disease and need professional support to achieve the same lifestyle and risk-factor targets. EUROACTION was a family-centred programme and actively involved patients' partners and other family members. A family intervention is appropriate because married couples show concordance for lifestyle, and concordance for change.[33,34] Those patients making the greatest changes had partners making similar changes.

EUROACTION was coordinated by nurses because of evidence that nurse-managed programmes improve lifestyle, risk factor control, use of medications, and quality of life.[35–41] The basis of EUROACTION was lifestyle change—ie, avoidance of tobacco, achievement of a healthy diet, and physical activity, which were all given equal weighting. For patients with coronary disease, supervised exercise was needed in the early stages, which was the role of the physiotherapist, but in primary care, nurses promoted physical activity in high-risk patients without supervision. They achieved an increase in physical activity without any adverse effects. Total risk assessment and management was a central principle of EUROACTION for both coronary heart disease and high-risk (as identified by SCORE) patients. So in addition to promotion of all aspects of a healthy lifestyle, comprehensive risk-factor management and appropriate use of cardioprotective drugs were all addressed. The EUROACTION programme did not use specialised hospital or community facilities; simple equipment was used for supervised exercise sessions so that the exercises could be replicated at home. As a consequence EUROACTION can be set up in any hospital or general practice without dedicated facilities.

A matched, paired cluster-randomised controlled trial has inherent limitations. Our study was statistically underpowered for three reasons. First, the number of patients and partners recruited was much smaller than expected. Second, although pairs of centres were matched, initial patient assessment revealed some unexpected differences in patient characteristics in both directions—ie, some favoured usual care and some favoured intervention. Third, heterogeneity between pairs of centres for some results which, given the small number of pairs, also reduced our power. Some of the differences in favour of intervention—eg, prevention of smoking relapse in patients with coronary disease, are still clinically important but not significant. Our analysis was by intention to treat because all patients and partners identified at baseline, irrespective of eligibility or participation, were invited back at 1 year. An underestimation of treatment effect is possible for three reasons. First, centres randomised to usual care knew they would be audited which might have led to improved practice. Second, a random subsample of usual-care patients had a comprehensive baseline assessment alerting them and their doctors to the need for change. Third, almost a fifth of usual-care patients received some form of structured cardiac rehabilitation that will have had some similarities to EUROACTION interventions. Overestimation of treatment effect might have occurred because not all those at baseline in the intervention groups came back at 1 year. These non-responders included a higher proportion of heavy smokers, obese, and sedentary patients than in the responders. However—the same bias is also true for usual care—of all those patients identified at baseline, slightly more than half came at 1 year. We know from other studies that non-responders tend to have unhealthier lifestyles and

poorer risk factor control. After all these caveats are taken into account, the EUROACTION programme, in both hospital and primary care, has shown real improvements in lifestyle, risk-factor control, and use of cardioprotective drugs compared with usual care. As well as showing the clinical effectiveness of the EUROACTION programme, we also have to answer the question is the EUROACTION programme cost effective? A cost-effectiveness analysis will be reported separately.

In conclusion, EUROACTION has shown that standards of preventive care in general hospitals and general practices across Europe can be improved. This nurse-coordinated, multidisciplinary, family-based, ambulatory programme achieved healthier lifestyle changes and improvements in other risk factors for patients with coronary heart disease and those at high risk of cardiovascular disease and their partners than those in usual care. EUROACTION is a model of preventive cardiology, which has been successfully implemented and assessed, and can be used in routine clinical practice. To achieve the effects of EUROACTION we need to go beyond specialised cardiac rehabilitation services and provide local preventive cardiology programmes, appropriately adapted to the medical, cultural, and economic setting of a country.

Contributors

A scientific steering group approved the protocol and study design and was responsible for the scientific integrity of the study. The national coordinators for each country were also members of the steering committee; they were responsible for identifying and recruiting the hospitals and general practices, obtaining ethics committee approval, appointing and supervising staff in the centres, and contributing scientifically to the publication of results. DAW was the principal investigator and led the central coordinating team. DAW, GDB, KK, and DDB contributed to the study design and development of the scientific protocol. KK and CJ participated in the development of case record forms. KK was the medical coordinator for the study. CJ was the research nurse coordinator for the study and participated in the set up and development of the intervention. AM participated in the development, coordination, and analysis of the dietetic part of the study. JJ and AH participated in the development, coordination, and analysis of the physiotherapy and physical activity parts of the study. SC had overall responsibility for data collection and quality assurance. GDB led the statistical centre. DDB was the statistician at the statistical centre. DAW, DDB, GDB, KK, TC, and SC participated in the statistical analyses. DAW, DDB, GDB, KK, TC, SC, and OF participated in the interpretation of the data. DAW, DDB, GDB, KK, CJ, TC, SC, and OF participated in the writing of the report. All authors have seen and approved the final version of the report for publication.

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Conflict of interest statement

DAW and OF are paid consultants to AstraZeneca advisory boards and have received honoraria for speaking at AstraZeneca-sponsored meetings. GDB and DAW have received research grants from AstraZeneca, and GDB from Solvay. AM is a member of the advisory board of Flora. The other authors declare that they have no conflict of interest.

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Appendix 3:

EUROACTION: List of author's publications

Appendix 3: List of Relevant Publications

Peer review journal articles:

- Wood, D.A, Kotseva, K., Connolly, S, Jennings, C, Mead, A, **Jones**, **J**, Holden, A, De Bacquer, D, Collier, T, De Backer, G, Faergeman, O. on behalf of EUROACTION Study Group (2008) Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet*, 371: 1999–2012.
- Wood, D.A, Kotseva, K., Jennings, C, Mead, A, **Jones**, **J**, Holden, A, Connolly, S, De Bacquer, De Backer, G. on behalf of the EuroAction Study Group (2004). EUROACTION: A European Society of Cardiology demonstration project in preventive cardiology: A cluster randomised controlled trial of a multi-disciplinary preventive cardiology programme for coronary patients, asymptomatic high risk individuals and their families. Summary of design, methodology and outcomes. *Eur Heart J Suppl*, 6: j3-j15. (IF 2004 6.247*) ISSN:1520-765X*

Books:

- Jennings C; Mead A; **Jones JL**; Holden A; Connolly S; Kotseva K; Wood D (2009). **Preventive Cardiology**. Oxford University Press.

Other journal articles:

- **Jones, J.** (2007) Preventive cardiology– success in getting Europe more physically active. *HealthEx*, 13(Jul):12-15

Abstracts (lead author):

- Jones, J. et al., (2007) EUROACTION: The effectiveness of a 1-year preventive cardiology programme in general practice to achieve the lifestyle goals in cardiovascular disease prevention. *European Journal of Cardiovascular Prevention and Rehabilitation, Vol 14 (Suppl 1), S68.*
- Jones, J. et al., (2006) EUROACTION: Achieving Lifestyle and Behaviour Targets in a 16 week nurse-led multidisciplinary cardiovascular prevention and rehabilitation hospital programme. *Journal of Cardiopulmonary Rehabilitation, 26 (4), 251.*
- Jones, J. et al., (2006) EUROACTION: A nurse-led multidisciplinary cardiovascular prevention and rehabilitation hospital programme. 16 week results. *Journal of Cardiopulmonary Rehabilitation, 26 (4), 251.*
- Jones, J. et al., EUROACTION: The Baseline Challenge for a Cardiovascular Prevention programme in Primary Care. *Journal of Cardiopulmonary Rehabilitation, 26 (4), 258.*
- Jones, J. et al., (2006) EUROACTION: A cardiovascular prevention and rehabilitation programme - the hospital physical activity intervention results. *European Journal of Cardiovascular Prevention and Rehabilitation, Vol 13 (Suppl 1), S52*
- Jones JL; Mead A; Jennings CS; Holden A; Connolly SB; Kotseva K; Collier T; De Bacquer D; De Backer G; Wood DA. EUROACTION: Changes in smoking, diet and physical activity over one-year in a family based preventive cardiology programme in hospital and general practice. *World Congress of Cardiology*, 118:E433-E434. Lippincott Williams & Wilkins.
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Abstracts (co-author):

- Kotseva K; Connolly SB; Jennings C; Mead A; Jones J; Holden A; Collier T; De Bacquer D; De Backer G; Wood D. (2007). EUROACTION: A European Society of Cardiology demonstration project in preventive cardiology - one year results for coronary patients and their partners. *Journal of Human Hypertension.* 21:841-842.
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Appendix 4:

Methods – Advantages and Disadvantages

Appendix 4a: Advantages and Limitations of Physical Activity and Exercise Measures (Jennings et al., 2009)

	Advantages	**Limitations**
Doubly labelled water	▪ Precision of measure ▪ Non-invasive ▪ Ability to assess total energy expenditure	▪ Expensive
Self report methods of physical activity *e.g. seven day activity recall*	▪ Easy to administer ▪ Takes little time ▪ Inexpensive ▪ Low participant burden ▪ Can estimate energy expenditure from daily living	▪ Reliability and validity problems associated with recall ▪ Tendency for overestimation of activity ▪ Suitability of questionnaires varies in different populations
Accelerometers	▪ More objective indicator of body movement (accelerometers) ▪ Provides indicator of intensity, frequency and duration ▪ Inexpensive ▪ Minute by minute information and can record data for periods of time (weeks) ▪ Non invasive	▪ Financial cost ▪ Inaccurate assessment of a large range of activities (e.g. upper body, water-based activities ▪ Cannot guarantee accurate placement of monitor
Pedometers	▪ Inexpensive ▪ Non invasive ▪ Practical and easy in a number of settings ▪ Potential to promote behaviour change	▪ More objective indicator of body movement (accelerometers) ▪ Unable to detect intensity so loss of accuracy when jogging or running ▪ Possibility of participant tampering ▪ Limited to walking based activity

Appendix 4a *continued*: Advantages and Limitations of Physical Activity and Exercise Measures (Jennings et al., 2009)

	Advantages	**Limitations**
Aerobic capacity e.g. *cardiopulmonary exercise testing*	▪ Objective ▪ Valuable information for exercise prescription *(e.g. prognosis, risk stratification for exercise training)*	▪ Time consuming ▪ Associated risk (maximal testing) ▪ Not necessarily an indicator of habitual activity ▪ More invasive
Muscle strength	▪ Easy and simple to test	▪ Risk associated (1 repetition maximum) ▪ Not necessarily an indicator of cardiorespiratory fitness
Flexibility	▪ Easy and simple ▪ Inexpensive	▪ Not necessarily an indicator of cardiorespiratory fitness
Heart rate	▪ Easy and simple ▪ Inexpensive	▪ Modified by many extrinsic factors *(e.g. temperature, caffeine, medications etc)*
Body composition	▪ Easy and simple to measure ▪ Indirectly can indicate activity participation	▪ BMI does not take increased lean mass into consideration ▪ Bioelectric impedance influenced by hydration status ▪ Inhibitory factors in measurement of body folds

Appendix 4b: Submaximal tests for functional capacity in a preventive cardiology programme (Jennings et al., 2009)

	Examples	**Brief description**	**Main advantages**	**Main limitations**
Walking-based tests	6 Minute Walk Test (6-MWT)	▪ Non-incremental self paced test over a 25 meter track ▪ Metres per minute, heart rate and exertion level recorded for a 'comfortable' walking speed each minute for a period of 6 minutes. ▪ Score includes - Total metres scored, average metres per minute, average MET score and number and length of rest periods where indicated.	▪ Familiarity of activity ▪ Particularly suitable for the low capacity individual	▪ Unable to assess response to incremental workloads ▪ Performance influenced by extrinsic factors (e.g. motivation)
	Incremental Shuttle Walk Test (ISWT)	▪ Designed originally for COPD patients ▪ External pacing of incremental walking speeds around a 10 meter length ▪ Score includes total metres scored, MET score and heart rate and exertion level for fixed submaximal workloads	▪ Familiarity of activity ▪ Incremental and able to assess heart rate and exertion for increasing intensity ▪ Assist in familiarising the rating of perceived exertion scale	▪ Inherent warm up period provided as initial speeds are very slow ▪ 1 minute intervals and therefore unable to assess steady state

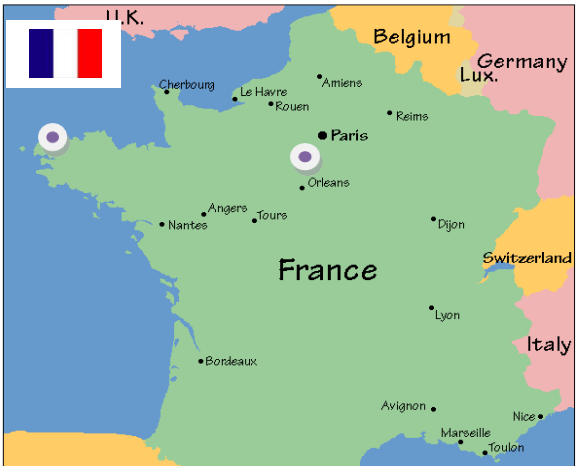
Appendix 4b *continued*: Submaximal tests for functional capacity in a preventive cardiology programme (Jennings et al., 2009)

	Examples	**Brief description**	**Main advantages**	**Main limitations**
Stepping tests	Chester step test (adapted)	▪ External pacing of incremental stepping onto and off of a step of known height ▪ Score includes total minutes achieved, METs score and heart rate and exertion level for fixed submaximal workloads	▪ Incremental and able to assess heart rate and exertion for increasing intensity ▪ Assist in familiarizing the rating of perceived exertion scale ▪ 2 minute increments so more likely to achieve steady state responses	▪ Unsuitable for individuals with orthopedic restrictions ▪ Degree of coordination required
Cycle test	Monarch bike test	▪ Incremental workload at 2 minute intervals ▪ Score includes total minutes achieved, METs score and heart rate and exertion level for fixed submaximal workloads	▪ Suitable for individuals with poor balance or restrictions in weight bearing activities ▪ Incremental and able to assess heart rate and exertion for increasing intensity ▪ Assist in familiarizing the rating of perceived exertion scale ▪ 2 minute increments so more likely to achieve steady state responses	▪ Less familiar activity for some individuals ▪ Unsuitable for individuals with reduced knee or hip range of movement ▪ Degree of coordination required

Appendix 5:

EUROACTION Centres

Appendix 5: The 24 EUROACTION centres



Hospital arm – INTERVENTION centre
Institut Hospitalier Jacques Cartier, France

Hospital arm – USUAL CARE centre
Hospitalier Yves Le Foll, France

General practice arm – USUAL CARE centre
Via S Valentino 20, 33100 Udine, Italy

General practice arm – INTERVENTION centre
Rive dai Stimatinis 12, 33013 Gemona del Friuli, Italy

Hospital arm – INTERVENTION centre
Boldrini Hospital, Italy

Hospital arm – USUAL CARE centre
San Paolo Hospital, Italy

Hospital arm – USUAL CARE centre
Powiatowy Szpital w Olkuszu, Poland

Hospital arm – INTERVENTION centre
Jagiellonian University Medical College, Krakow, Poland

General practice arm – INTERVENTION centre
Centrum Medycyny Profi laktycznej w Krakowie, Poland

General practice arm – USUAL CARE centre
Podstawowa Opieka Zdrowotna—
Szpital Uniwersytecki w Krakowie, Poland

Appendix 5: The 24 EUROACTION centres *continued*

Hospital arm – INTERVENTION centre
Hospital Universitario Dr Peset, Spain

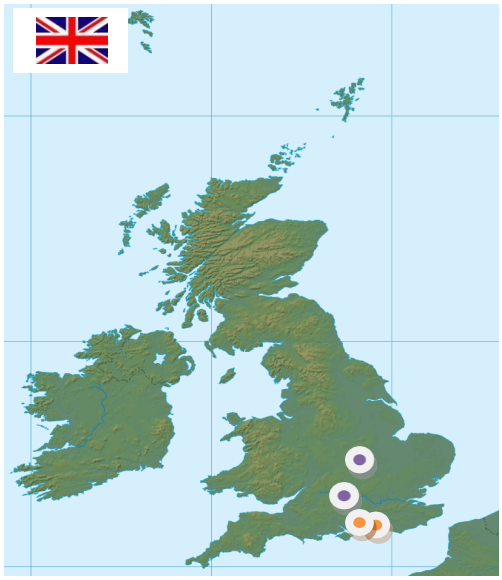
General practice arm – INTERVENTION centre
Centro de Salud Salvador Pau, Valencia, Spain

General practice arm – USUAL CARE centre
Centro de Salud de Manises, Valencia, Spain

Hospital arm – USUAL CARE centre
Hospital General Alicante, Spain

Hospital arm – USUAL CARE centre
Uddevalla Hospital Medicinkliniken, Sweden

Hospital arm – INTERVENTION centre
Halmstad Hospital, Sweden



Hospital arm – INTERVENTION centre
Stoke Mandeville Hospital, UK

Hospital arm – USUAL CARE centre
Queen Mary Hospital Sidcup, UK

General practice arm – INTERVENTION centre
Seaside Medical Centre, Eastbourne, UK

General practice arm – USUAL CARE centre
Green Street Clinic, Eastbourne, UK

Appendix 5: The 24 EUROACTION centres *continued*

General practice arm – INTERVENTION centre
Sundhedscenteret Skanderborg, Denmark

General practice arm – USUAL CARE centre
Gasvej 5, 8700 Horsens, Denmark

General practice arm – INTERVENTION centre
Gezondheidscentrum Hoensbroek-Noord, Netherlands

General practice arm – USUAL CARE centre
Gezondheidscentrum Neerbeek, Netherlands

Appendix 6:

Patient consent and information forms

Information sheet for coronary patients

EUROACTION project

Explanation

We would like to invite you to participate in a research project. You should not take part in the study if you do not wish to do so. If you decide to participate, please let us know beforehand if you have been involved in any other study during the last year. If you decide not to take part your treatment will not be affected by your decision. You are free to withdraw at any time without explanation and your subsequent treatment will not be affected.

As you know you were admitted to the hospital for treatment for your heart condition. Your hospital is taking part in a European survey of patients who have been treated in hospital for the same reason and we would be most grateful if you could answer some questions about your lifestyle and if we could measure your height, weight and blood pressure and take a blood sample from you.

The purpose of the survey, which is co-ordinated by the European Society of Cardiology and National Heart and Lung Institute in London, is to find out how you, and patients like you, are being looked after throughout Europe and to find ways of improving the care given to patients. All information collected about your medical condition will remain strictly confidential under the Data Protection Act and will be available only to your GP, your hospital Consultant and to National Heart and Lung Institute.

If you need more information please contact……..on……..

We hope you will feel able to help in this European survey. Thank you for your help with this medical research.

Patient consent form

EUROACTION project

The participant should complete the whole of this sheet him or herself

Please tick each statement if it applies to you

I have read the Information Sheet for Patients ☐

I have been given the opportunity to ask questions and discuss the study ☐

I have received satisfactory answers to all my questions ☐

I have received enough information about the study ☐

The study has been explained to me by:

Prof/Dr/Mr/Mrs/Ms……..

I understand that I am free to withdraw from the study at any time Without having to give a reason for withdrawing and without affecting my future medical care ☐

I agree to take part in this study. ☐

Signed…….Date……..

(Name in block capitals)……..

Investigator's signature……..Date……

(Name in block capitals)……

EuroAction
for our hearts

Appendix 7:

Competency checklist for sub-maximal exercise testing

Appendix 8a: COMPETENCY CHECKILIST FOR THE INCREMENTAL SHUTTLE WALK TEST PROTOCOL

Competency **√** = competent **A** = competent but action point recommended **X** = not yet competent		**Comments**
Was all the equipment set up correctly before the test?		
Was the pre-test checklist completed?		
Was an appropriate end point determined and calculated?		
Was the heart rate monitor fitted appropriately?		
Were pre-exercise HR and BP collected appropriately?		
Was RPE familiarised correctly?		
Was there a pre-test explanation that included: _ Purpose _ Incremental, levels _ Walking and bleeps etc _ At the end of each level HR, RPE and walk a little faster _ Normal S & S _ Warnings? _ Test end point _ Safety		
Was consent to participate reaffirmed?		
Did the tester walk with the client for the first level and then withdraw?		
Did the tester use standardised encouragement and discourage talking		
Did the tester warn the next level approaching (cue effectively) and provide appropriate instruction?		

Were HR and RPE collected at the correct times in the test?		
Was the client well observed during the test?		
Was the tester appropriately positioned during the test?		
Did the tester use volume and pitch of voice effectively?		
Did the tester check regularly on the participant's ability to cope with test?		
Did the tester give clear and understandable verbal instruction?		
Was the test stopped appropriately?		
Did the client perform a short cool down?		
Was recovery monitored appropriately?		
Was the test scored correctly and documented clearly?		
Was the test data correctly entered into the database?		

Appendix 8b: COMPETENCY ASSESSMENT FOR CHESTER STEP TEST PROTOCOL

Competency	**√** = competent **A** = competent but action point recommended **X** = not yet competent	**Comments**
Was all the equipment set up correctly before the test?		
Was the pre-test checklist completed?		
Was an appropriate end point determined and calculated?		
Was the heart rate monitor fitted appropriately?		
Were pre-exercise HR and BP collected appropriately?		
Was RPE familiarised correctly?		
Was there a pre-test explanation that included: - Purpose - Incremental, levels of 2 mins stages - Stepping Rate and Step Height - At the end of each stage HR, RPE observation of Normal S & S - Warnings? - Test end point - Safety of test overall		
Was consent to participate reaffirmed?		
Did the tester familiarise the individual to correct stepping technique and check ability to step with right and left side?		
Was the correct step height selected?		
Was the step positioned appropriately?		

Did the tester step with the client to correct any mismatch in pace with the recording/metronome		
Did the tester use standardised encouragement and discourage talking?		
Did the tester warn the next level approaching (cue effectively) and provide appropriate instruction?		
Were HR and RPE noted every 30 to 45 seconds and then collected at the correct times at the end of each stage? Was HR & RPE noted down with 15-20 seconds before end of stage before the pace was increased?		
Was the client well observed during the test?		
Was the tester appropriately positioned facing the patient during the test?		
Did the tester use volume and pitch of voice effectively?		
Did the tester check regularly on the participant's ability to cope with test?		
Did the tester give clear and understandable verbal instruction?		
Was the test stopped appropriately?		
Did the client perform a short cool down?		
Was recovery monitored appropriately?		
Was the test scored correctly and documented clearly?		

Appendix 8:

The warm-up

Appendix 8:

The warm-up component in the hospital-based supervised exercise intervention

1. Mobility exercises
Gradual progression of range of motion exercises to stimulate the release of synovial fluid. The mobility exercises were interspersed with gentle pulse raising movements.

2. Pulse raising movements
Progressive movements, using the large muscle groups, designed to gradually raise the intensity of myocardial workload. These pulse raising activities raised the heart rate to 20bpm below target heart rate and RPE no higher than 11 on the 6-20 scale.

3. Preparation stretches were interspersed with pulse raising activities to ensure that there were no significant decreases in heart rate.

4. Re-warm
The warm-up finished with pulse-raising movements to re-elevate the heart rate before the conditioning component began.

The standardised warm-up used:

SEQUENCE 1	**Examples of Teaching / Coaching Points**
Posture check	Posture check. Feet hip distance apart, back in a neutral position, shoulders back with the ears over the shoulders. Stand tall as if you are being pulled through the spine to the ceiling. Breathe in and as you breathe out pull your abdominals into your back bone. Release this tension by 50% and maintain this posture while performing the exercises.
March time	
Alternate toe taps	Heel stays away from the floor.
March time	
Alternate heel digs	Only the heel goes down.
March time	
Alternate knee raises - leg bent to 45 degrees to hip	Lift knee towards the trunk – maintain a good posture, taking care not to lean forward. Offer support or demonstrate toe taps for those with compromised balance.
March time	
Alternate legs to side	Keep the weight over the supporting leg avoid transferring weight onto the leg that you are moving out to the side - just touch the floor with the ball of the foot.
March time	
Alternate toe tap behind	The toe touches the floor but the heel remains high. Weight remains central over the supporting leg, ensuring the front knee remains in line with the foot.
March on spot	

• Shoulder rolls - forward & back	Make as big a circle as you can. Try not to involve the head or trunk - only the shoulder and arm should be moving.
• Shoulder shrugs - up and down	Keep the head still - just the shoulders move in a smooth and controlled way.
Stand feet apart	
• Lateral flexion – alternate right & left	As you bend to each side, support your weight by placing a hand on the outside of the thigh over which you are bending. Try not to lean forward or back. Always maintain a good posture and return to the centre before bending to the other side, Do <u>not</u> bounce in an effort to bend further over.
• Spinal rotation – alternate right & left	Hips must be facing forward all the time; only your top half should move. Do not swing round from one side to another - return to the centre between each twist
Walk around the room at normal pace	Maintain a good posture. Walk with a heel toe strike

SEQUENCE 2	
March on spot	
Alternate toe taps – with bicep curl. Supporting leg bending a little deeper	Elbows into the body arms bend in a controlled manner. Keep the knee of the bent leg over the shoe laces
March on spot	
Alternate heel digs - with bicep curl. Supporting leg bending a little deeper	
March on spot	
Alternate knee raises – 90 degrees to hip. Add a small knee tap with hand	
March on spot	
Alternate legs to side – raise ‘matching’ arm to side. Supporting leg bending a little deeper	Keep arm at hip level
March on spot	
Alternate toe tap behind - raise ‘opposite’ arm to front	Keep arm at waist level
March on spot	
• Shoulder rolls - forward & back with hand on shoulder	
Stand feet apart	
• Lateral flexion – alternate right & left	
• Spinal rotation – alternate right & left	
Walk around the room at a slightly brisker pace	

SEQUENCE 3	
March on spot	
Alternate toe taps – deeper bend of the supporting leg. Raise arms to chest height	
March on spot	
Alternate heel digs – deeper bend of the supporting leg. Raise arms to chest height	

March on spot	
Alternate knee raises – to opposite hand. Slightly bigger movement of the arms	Lift knees to hip height increase the intensity of the move by a larger movement of the arms
March on spot	
Alternate legs to side – raise both arms to side to waist height	
March on spot	
Alternate toe tap behind – raise both arms to front to chest height	
March on spot	
Shoulder rotation -'brush hair' alternate sides	
Walk around the room at a brisker pace	

STRETCHES
March on spot – top of back stretch (trapezius) • Bring your arms around in front of the body as if hugging a large person. Drop your head down to look at your feet. Feel a gentle tension at the top of the back
Heel digs – back of upper arm stretch (triceps) • Check your posture. Place your left hand onto your left shoulder and slide the hand down your back. Support your left arm with your right hand. Only go as far as is comfortable. If the shoulder is painful or lacks mobility take the arm across the chest slightly raised. Tension should be felt on the upper back of the raised arm. Repeat on the right arm.
March on spot – front of chest stretch (pectoralis major) • Place the hands on the back of the hips and gently draw the elbows together until a slight tension is felt across the chest. Keep the back straight and the abdominals tight. Don't allow your chin to poke forward.
Toe tap behind into **Calf stretch (gastrocnemius)** • Keep weight central and extend the left leg to the back. Gently ease the heel into the floor, making sure the heel of your back foot is down and the toe is pointing forwards - not out at an angle. Take the weight forward onto the right leg until a gentle tension is felt in the calf of the left leg. Repeat on the right. Ensure knee of front leg remains in line with the foot.
Heel dig to the front into **Back of upper leg stretch (hamstring)** • Stand with feet hip distance apart. Bend the knees as if sitting on a stool and straighten one leg out to the front, taking care not to place any weight on it. With the weight over the bent leg and supporting the upper body by placing the hands onto upper thigh. Lift the bottom to increase the stretch, keeping the back in natural alignment. Keep the abdominal muscles tight and the back in a straight line with the eyes looking towards the floor. Avoid looking up. If necessary, use the wall for balance.
Front of upper thigh stretch (Quadriceps) – with support • Keeping the thighs together and the knees in a straight line, lift the left foot up towards your bottom until the tension is felt at the front of the thigh. Hold your leg in this position either by holding the foot with your hand or by holding the bottom of your trousers. Keep knees in line. Take care to maintain a good posture and not arch your back. Repeat on right leg
Re-warm - Brisk walk around room

Appendix 9:

Supplementary results

Appendix 9: Supplementary results

Appendix 9a: HOSPITAL STUDY

Summary of physical activity results in coronary patients – at 1-year, ranked by country (highest to lowest status)

7-DAR *(SUBJECTIIVE PHYSICAL ACTIVITY PARTICIPATION)*	Sweden INT	France INT	UK INT	Poland INT	Sweden UC	Italy INT	Spain INT	Italy UC	France UC	UK UC	Poland UC	Spain UC
% Achieving EGPA	77% (1)	68% (2)	64% (3)	50% (4)	52% (5)	43% (6)	25% (7)	23% (8)	13% (9)	12% (10/11)	12% (10/11)	9.1% (12)

7-Day Pedometer *(OBJECTIVE PHYSICAL ACTIVITY PARTICIPATION)*	Italy INT	Sweden INT	UK INT	Spain INT	France INT	France UC	Poland INT	Sweden UC	Italy UC	UK UC	Poland UC	Spain UC
Mean steps per day	8975 (1)	8594 (2)	7970 (3)	7563 (4)	7523 (5)	6552 (6)	6390 (7)	6146 (8)	6072 (9)	5884 (10)	4816 (11)	3464 (12)

Incremental Shuttle Walk Test *(CARDIORESPIRATORY FITNESS)*	Italy INT	Sweden INT	UK INT	Sweden UC	France UC	France INT	Spain UC	UK UC	Poland UC	Poland INT	Spain INT	Italy UC
Mean metres scored	517 (1)	506 (2)	455 (3)	447 (4)	434 (5)	417 (6)	358 (7)	355 (8)	337 (9)	315 (10)	245 (11)	196 (12)

Appendix 9b: GENERAL PRACTICE STUDY
Summary of physical activity results in HRI – at 1-year, ranked by centre (highest to lowest status)

7-DAR *(PRIMARY END POINT)*	UK INT	Denmark INT	Poland INT	Netherlands INT	UK UC	Denmark UC	Netherlands UC	Spain INT	Italy INT	Italy UC	Spain UC	Poland UC
% Achieving EGPA	76% (1)	72% (2)	62% (3)	56% (4)	40% (5)	37% (6)	36.6% (7)	28% (8)	22% (9)	16% (10)	4.7% (11)	4.4% (12)

7-Day Pedometer	Poland UC	UK INT	Spain INT	Italy INT	Poland INT	Denmark INT	Netherlands UC	Netherlands INT	Spain UC	Denmark UC	UK UC	Italy UC
Mean steps per day	9171 (1)	8390 (2)	8186 (3)	7894 (4)	7886 (5)	7057 (6)	6972 (7)	6852 (8)	6496 (9)	6205 (10)	6049 (11)	5451 (12)

Chester Step Test	Denmark INT	Netherlands INT	Italy INT	Denmark UC	UK INT	Spain UC	Poland INT	Poland UC	Netherlands UC	UK UC	Spain INT	Italy UC
Time achieved	8.82 (1)	8.09 (2)	7.50 (3)	7.21 (4)	7.15 (5)	7.11 (6)	6.99 (7)	6.96 (8)	6.63 (9)	5.5(10)	5.45 (11)	5451 (12)

Appendix 9c: GENERAL PRACTICE STUDY
Summary of *changes* in physical activity from the initial assessment to 1-year – ranked by centre (greatest to lowest gains)

7-DAR *(PRIMARY END POINT)*	UK INT	Denmark INT	Netherlands INT	Poland INT	Spain INT	UK UC	Italy INT	Italy UC	Denmark UC	Netherlands UC	Spain UC	Poland UC
% Achieving EGPA	+52% (1)	+33% (2)	+30% (3)	+28% (4)	+3% (5)	+2% (6)	-3% (7)	-4% (8)	-8% (9)	-14% (10)	-18% (11)	-21% (12)

7-Day Pedometer	Spain INT	UK INT	Poland INT	Denmark UC	Netherlands INT	Denmark INT	Italy INT	Netherlands UC	Italy UC	Spain UC	Poland UC	UK UC
Mean steps per day	+2192 (1)	+1739 (2)	+1025 (3)	+1007 (4)	+957 (5)	+403 (6)	+387 (7)	+302 (8)	+94 (9)	+93 (10)	-89% (11)	-202% (12)

Chester Step Test	Netherlands INT	Poland INT	Italy INT	UK INT	Netherlands UC	Denmark INT	Denmark UC	Poland UC	Spain INT	UK UC	Spain UC	Italy UC
Time achieved	+1.46 (1)	+0.82 (2)	+0.5 (3)	+0.45 (4)	0.36 (5)	+0.34 (6)	+0.29 (7)	+0.2 (8)	-0.4 (9)	-0.97 (10)	-1.18 (10)	-1.27 (12)

Appendix 9d: HOSPITAL AND GENERAL PRACTICE STUDIES
Summary of results for the secondary objectives

Change between IA and EOP in physical activity participation	**COR INT** Δ IA to 16-weeks	**COR UC** Δ IA to 16-weeks	**HRI INT** Δ IA to 1-year	**HRI UC** Δ IA to 1-year
Subjective physical activity participation: **Change** in proportion achieving self-reported physical activity target from IA to EOP	+44.1% (+ 40.4% to +47.8%) P<0.0001	Not known	+23.5% (+2.2% to +44.8%)	-10.2% (-19.3% to -1.1%)
Difference in the difference in change over time between INT and UC	No evaluation possible		+32.9% (+11.8% to +53.9%); P=0.01	
Objective physical activity participation: Change in mean steps per day from IA to EOP	+1362.1 steps (+1127.2 to +1597.0) P<0.0001	Not known	+1107.1 (+356.5 to +1857.7)	+135.5 (-320.3 to +591.2)
Difference in the difference in change over time between INT and UC	No evaluation possible		+895.3 (-201.9 to +1992.5); P=0.09	
Change between IA and EOP in cardiorespiratory fitness Mean performance distance or minutes achieved	75.8 metres (+67.4m to +84.2m) P<0.0001	Not known	+0.47 (-0.08 to +1.03)	-0.42 (-1.25 to +0.41)
Difference in the difference in change over time between INT and UC	No evaluation possible		+0.94 (+0.23 to +1.66); P=0.02	

COR = coronary patients in hospital study HRI = high risk individuals in general practice study IA = initial assessment EOP = end of programme