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FULL RESEARCH PAPER
Prevention in practice

Randomized trial of cardiovascular prevention in Norway combining an in-hospital lifestyle course with primary care follow-up: the Hjerteløftet study

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Aims Cardiovascular risk factor control is suboptimal in Europe, including Norway. The present study examined the efficacy of a multimodal primary prevention intervention programme based on the existing Norwegian health care system.

Methods and results In this open-label randomized controlled trial, adult patients with elevated cardiovascular risk were randomly assigned to an intervention programme including a hospital-based lifestyle course and primary care follow-up or to a control group (CG). The participants were recruited between 2011 and 2015. Primary outcome was change in validated cardiovascular risk scores, national and international (NORRISK, NORRISK 2, Framingham, PROCAM) between baseline and follow-up. Secondary outcomes included major cardiovascular risk factors. After 36 months the NORRISK score was significantly improved in patients assigned to the intervention group (IG) compared to patients assigned to the CG; absolute difference in mean delta score in the IG ($n = 305$) compared to mean delta score in the CG ($n = 296$): −0.92, 95% CI: −1.48 to −0.36, $P = 0.001$. The results for NORRISK 2, Framingham and PROCAM showed similar significant effects. The secondary endpoints including total cholesterol and blood pressure were only minimally, and non-significantly, reduced in the IG, but the proportion of smokers ($P = 0.0028$) and with metabolic syndrome ($P < 0.0001$) were significantly reduced. A limited number of cardiovascular events were observed, IG ($n = 9$), CG ($n = 16$).

Conclusion In subjects with elevated cardiovascular risk, a newly developed prevention programme, combining a hospital-based lifestyle course and primary care follow-up, significantly reduced cardiovascular risk scores after 36 months. This benefit appeared achievable primarily through improvements in metabolic syndrome characteristics and smoking habits.

The study protocol was registered in ClinicalTrials.gov (NCT01741428).

Keywords Primary prevention • Cardiovascular disease • Cardiovascular risk • Metabolic syndrome • Smoking cessation • Lifestyle intervention

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Introduction

Cardiovascular diseases (CVDs) remain a leading cause of premature mortality and morbidity in the Western world[1] and the risk of suffering from CVDs is strongly related to the number, and lack of control, of cardiovascular risk factors.[2] There is a wealth of evidence that healthy lifestyle and control of blood pressure, lipids and glucose can prevent cardiovascular events.[3] Specific goals have been established for different risk factors, as stated in European and American clinical guidelines,[4,5] and with continuous adjustments towards lower levels as new evidence becomes available. Lifestyle interventions and drug treatment are complementary strategies that need to be put in action at the right stage in risk development. However, guidelines implementation is suboptimal as a large majority of patients in Europe with high CVD risk fail to achieve guideline-recommended targets for CVD prevention.[6,7] Barriers to implementation are many and different regions of the world have different challenges.[6] Consequently, effective strategies for improving primary prevention on CVD are still needed.

Prevention remains a major objective in a national strategy for reducing non-communicable diseases in Norway.[8] The Coordination Reform (2008–09) stated that there are insufficient efforts aimed at limiting and preventing disease in Norway's current health care system, because most of the capacity is bound up treating illness and repairing health. Further, it is pointed out that prevention and early intervention efforts often lose out in the battle for resources, where more specialized services tend to prevail.[9] The present study was initiated by the Norwegian health authorities in 2010 with an overall goal to learn more about how to manage effective prevention measures with basis in primary care.

The aim of the study was to develop, implement and evaluate a multimodal intervention programme for primary cardiovascular prevention, based on the existing health care system in Norway. The programme was designed to practice prevention according to national clinical guidelines among subjects with elevated CVD risk, identified by the NORRISK, a national developed risk algorithm parallel to the European SCORE.[10] The aim of the intervention was to improve CVD risk as quantified by the NORRISK score and similar international risk algorithms, as compared with a usual care group during a 36 months follow-up period.

A further aim was to evaluate the contemporary risk profile in the population and examine what risk factors are currently most important and most suitable for effective intervention.

Methods

Design

This trial was a randomized, open label, controlled trial, comparing an intervention group (IG) with a control group (CG) receiving usual care. The study was conducted according to the Helsinki Declaration and was performed in the period 2011–2019. The inclusion period was 22 August 2011—3 December 2015, and a total of 701 subjects were included. The study protocol was registered in ClinicalTrials.gov (NCT0174128) 30 November 2012, i.e. somewhat delayed due to technical reasons, when the first 225 patients had already been enrolled. Reporting follows the CONSORT 2010 statement.[11]

Setting and study participants

From May 2011, general practitioners (GPs) in the south and eastern part of Norway were invited to refer subjects with elevated risk. To ensure sufficient recruitment the area of referring GPs was later extended to the whole country. 850 GPs received written information about the study and the study staff visited 150 GPs at their office. The GPs were asked to identify patients judged to have a need of primary prevention and who were likely to benefit from participation in the programme. In addition, information about the study was promoted at several locations in the communities to reach possible participants directly (Healthy Life Centres, pharmacies, at workplaces with sedentary work). The study was also advertised in newspapers, radio and television. The patient could contact his GP who would assess the patient's risk and refer the patient. Study staff included consecutively eligible patients who signed an informed, written consent before inclusion in the study. Eligible patients were adults aged 35 to 67 years with elevated CVD risk defined by age-specific thresholds of >0.5, >2.5 and >5% in age groups <50, 50–59 and > 60 years, which corresponded to being 50% of the risk-threshold where pharmacological intervention was recommended according to the national clinical guidelines.[12] The calculation of CVD risk was performed using the published NORRISK algorithm,[10] a SCORE type model based on Norwegian data. The NORRISK score was obtained from an available computerized risk score calculator, where age, sex, total cholesterol (TC), systolic blood pressure (SBP), smoking habits and family history of CVD were standard inputs. Additionally, depending on the presence of the metabolic syndrome, i.e. the presence of three or more of the harmonized criteria,[13] the risk was multiplied with a factor of 1,4 as recommended in the national guidelines.[12] The exclusion criteria were as follows: Previous CVD, congenital heart disease, presence of valvular heart disease (interpreted as regarding only clinically relevant conditions), psychiatric or somatic disease restricting performing adequate physical activity or participation in the lifestyle course and presence of cancer with significantly reduced life expectancy.

Randomization and masking

Patients were randomly assigned (1:1) into one of two groups, receiving either intervention or usual care treatment strategies. A permuted block randomization was generated, and sealed opaque envelopes with consecutive inclusion numbers were made. The sequence was generated by Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital.

Outcomes and assessments

The primary endpoint was defined as the change in total CVD risk between baseline and 3 years follow-up as calculated by NORRISK,[10] the Framingham risk calculation[14] and by the German developed PROCAM risk score.[15] As a protocol amendment the corresponding change in NORRISK 2 was added as an endpoint, following the development of a revised and updated national risk algorithm,[16] that was implemented by the Norwegian health authorities from 2017 onward. Secondary outcome measures included change in SBP and diastolic blood pressure (DBP), serum lipids, HbA1c, and waist circumference.

Risk factor assessments were performed at baseline and after three years by the patients' GP, who submitted the results to study staff at the hospital. The NORRISK and PROCAM score were calculated by study personnel using online available computerized risk score calculators (www.legehandboka.no and www.assmann-stiftung.de, respectively). Framingham risk score and NORRISK 2 score were calculated through the published equations,[12,14] which were applied directly into the study database, and thus in a blinded manner, without possible influence from the study personnel.

Fatal and non-fatal cardiovascular events were registered and evaluated by an endpoint committee. The presence of metabolic syndrome

criteria, medication use, education level and occupational status was obtained by the GPs and registered by study personnel.

For a more thorough examination of the physiological effects of the intervention, a subset ($n = 255$) of the study-population were characterized in more detail with registration of self-reported and objectively measured physical activity levels, exercise capacity, electrocardiography, insulin, high-sensitive C-reactive protein, apolipoprotein A1, apolipoprotein B, body mass index, dietary habits and well-being at baseline and after 3 years. The results will be reported in a separate publication.

Intervention

Participants randomized to intervention participated in a 5-day lifestyle course at a specialized cardiac rehabilitation hospital (LHL-Hospital) (*Figure 1*). A multidisciplinary team consisting of physician, dietician, physiotherapist and nurse was responsible for the programme which was performed in groups of 6–15 participants. The three-year follow-up period was allocated to primary care and included a digital follow-up from the cardiac rehabilitation hospital. The intervention programme was based on the national clinical guidelines of cardiovascular prevention.[12]

5-day in-hospital programme

The programme focused on nutrition, physical activity, smoking cessation, stress management, motivation, and individual goal-setting. The programme consisted of both individual counselling, educational and experimental sessions, and the stages-of-change model of behavioural change was used as theoretical basis for the educational programme.[17] All patients in the IG performed a cardiopulmonary exercise test and went through a clinical examination. If indicated, patients were referred for further examinations and treatment. Patients received information about their exercise capacity and their baseline CVD risk and were given guideline-based recommendations for lifestyle changes and drug treatment.

Nutrition

The nutritional intervention aimed to develop the patient's awareness about healthier food choices and to provide learning tools to help them develop and maintain healthy behaviour. As primary care would play the main role during follow-up the counselling was in accordance with the Norwegian food-based dietary guidelines based on Nordic recommendations,[18] with focus on a varied diet with plenty of vegetables, fruit and berries, whole grain products and fish, and limited amounts of processed meat, red meat, salt, and sugar. A trained dietician was responsible for the diet counselling. The intervention also consisted of practical sessions focusing on labelling and exploring recipes and cooking habits. During the 5-day course, the participants made their own, individual dietary plan for the follow-up period, based on recommendations given and the participant's motivation for dietary change.

Exercise

The exercise intervention aimed to educate participants about the benefits of exercise and the safety of exertion despite the presence of cardiovascular risk factors. The theoretical sessions covered topics as motivation for exercise, benefits for health, how to perform exercise and the negative effects of inactivity. Based on the results of the cardiopulmonary exercise test the patients received individual advice on recommended exercise. Exercise sessions consisted of aerobic exercises, interval training, resistance training, aqua-aerobics, and attention training. The purpose of the activity-programme was to introduce the participants to a wide spectrum of activities and sports to make it more likely they would find an activity of interest, which they would be able to continue in the future. The participants' physical activity level and readiness to change was assessed, and during the 5-day course they made a graded physical activity plan for the follow-up period themselves, with support from study staff, tailored to the participants' lifestyle, motivation for change and physical activity level. The participants were encouraged to provide overview of local physical activity opportunities and make appointments before leaving the course. Both the type of activity, the frequency, intensity, and the duration of the activity sessions during the follow-up period were decisions made by the patient.

Stress-management

This section aimed at increasing patients' awareness of how behaviours and thoughts affect our health, providing motivational and psychological tools to help them develop and maintain healthier lifestyles as well as developing stress management coping skills for increased psychological well-being. The educational sessions were based on social cognitive theories.[19]

Smoking-cessation

Smokers, and patients who had recently quit tobacco use, were invited to attend a smoking-cessation course. The course provided information about the harmful effects of smoking, strategies to address withdrawal symptoms and to prevent relapses. The participants were offered pharmacological supporting therapy and had to decide a date for quitting tobacco use.

Goal setting

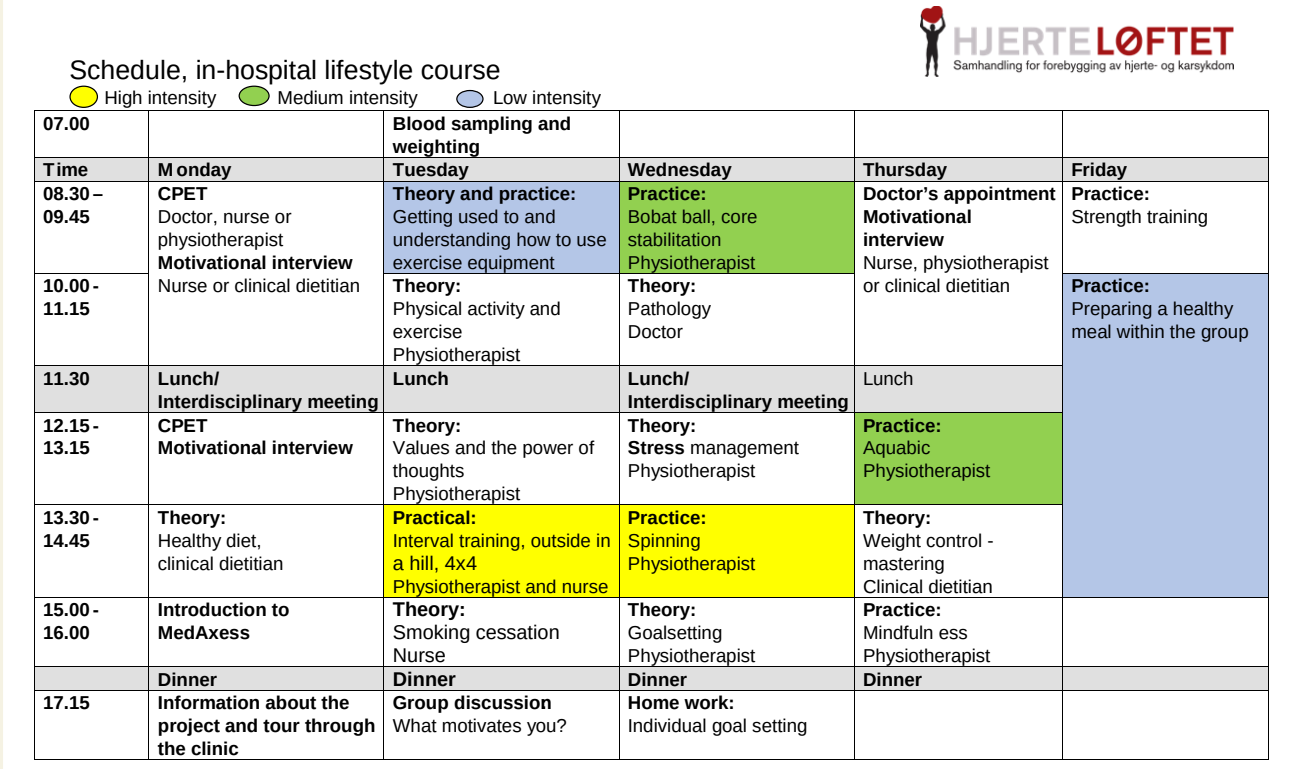
The participants were asked to establish individual, ambitious, but realistic goals for lifestyle changes.[20] They were encouraged to create a personal plan for the follow-up period containing self-administrated and/or group-based activities depending on personal interests and opportunities in their home area. The participants were also asked to make an appointment with a person (mentor) who could help them focus on their goals throughout the follow-up period. This mentor could be a private relation or a health care professional in primary care.

Digital follow-up

In order to help the participants focus on their goals and to facilitate social support[20] they were introduced to a digital communication follow-up tool. The participants were periodically (after 6 weeks, 3, 6, 9, 12, 18, 24, and 30 months) asked to report about their goal achievement and challenges, and they received short, tailored, individualized motivational feedback from study personnel at the coordinating cardiac rehabilitation hospital. The patients could communicate electronically with each other and could submit questions to the study staff and would receive an individual answer. They received newsletters four times a year and had access to a website with relevant information.

Primary care follow-up

The 3-year follow-up was an implementation phase, based on the personal plan for achieving and maintaining risk factor control decided at the lifestyle course. The results of the medical examination including recommendations for drug treatment and lifestyle changes were sent to the participant and the participant's GP. The GP was also informed about the participant's individual goals, plan for lifestyle changes and choice of mentor. Recommendations for follow-up intervals by the GP were given, but the actual follow-up routine decision was left to the GP. Similarly, any need for adjustments in the cardiovascular drug treatment was left to the GP. The decision regarding the duration and frequency of interaction between the participant and his mentor was left to the participant.



07.00		**Blood sampling and weighting**			
Time	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**
08.30 – 09.45	**CPET** Doctor, nurse or physiotherapist **Motivational interview** Nurse or clinical dietitian	**Theory and practice:** Getting used to and understanding how to use exercise equipment	**Practice:** Bobat ball, core stabilitation Physiotherapist	**Doctor's appointment** **Motivational interview** Nurse, physiotherapist or clinical dietitian	**Practice:** Strength training
10.00 - 11.15		**Theory:** Physical activity and exercise Physiotherapist	**Theory:** Pathology Doctor		**Practice:** Preparing a healthy meal within the group
11.30	**Lunch/ Interdisciplinary meeting**	**Lunch**	**Lunch/ Interdisciplinary meeting**	Lunch	
12.15 - 13.15	**CPET** **Motivational interview**	**Theory:** Values and the power of thoughts Physiotherapist	**Theory:** **Stress** management Physiotherapist	**Practice:** Aquabic Physiotherapist	
13.30 - 14.45	**Theory:** Healthy diet, clinical dietitian	**Practical:** Interval training, outside in a hill, 4x4 Physiotherapist and nurse	**Practice:** Spinning Physiotherapist	**Theory:** Weight control - mastering Clinical dietitian	
15.00 - 16.00	**Introduction to MedAxess**	**Theory:** Smoking cessation Nurse	**Theory:** Goalsetting Physiotherapist	**Practice:** Mindfuln ess Physiotherapist	
	Dinner	**Dinner**	**Dinner**	**Dinner**	
17.15	**Information about the project and tour through the clinic**	**Group discussion** What motivates you?	**Home work:** Individual goal setting		

Figure 1 Schedule, in-hospital lifestyle course. CPET, cardiopulmonal exercise test.

Usual care

The CG received usual care from their GP and did not get any specific advice from the study staff. The participants went through a baseline assessment. They were informed about their CVD risk status and that they would be contacted after 3 years for follow-up assessments.

Sample size and power estimation

We estimated the variability of the NORRISK score based on the analysis of the consecutively first 30 patients included. The estimated variability of the score difference corresponded to a standard deviation = 6.18%. We considered that an absolute difference in score of 1.5% would be of clinical interest as a reduction in cardiovascular mortality in this magnitude would be comparable to what has been reported for other important primary prevention interventions. For example, a similar effect was observed after 10–15 years for statins in the extended WOSCOPS study, that found death from all cardiovascular causes in the entire follow-up period was reduced from 9.0 to 7.6% vs. placebo.[21] For a power of 90% and a type-I error of 5% we needed 358 patients in each arm, 716 in total, to detect a difference between groups of this magnitude in risk score change between baseline and 3-year follow-up. A de facto power analysis confirmed our á priori estimation done at the beginning of the study. We have 90% power for an absolute difference in score of 1% considering a type-I error of 5%, the pooled standard deviation of the delta variable = 3.7605 and the sample size of 300 in each arm.

Statistical methods

Categorical variables were summarized as frequencies and continuous variables by the mean with its standard deviation. For the primary endpoints, NORRISK score, NORRISK 2, Framingham and PROCAM risk score, we evaluated the change in score from baseline to follow-up at 3 years. To control for baseline imbalance we used analysis of covariance (ANCOVA), which is a regression method relating outcome score to baseline score in each group.[22] Correlation between baseline and follow-up measurements was checked, as the efficiency gains of ANCOVA compared with a change score are low in presence of high correlation ($r > 0.8$). Logarithm transformation of continuous variables was performed to stabilize the model and check the results as far the significance. The secondary endpoints, SBP, DBP, TC, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides (TG) were analyzed in the same manner as the primary endpoint.

An 'on treatment' analysis was performed, followed by an 'intention-to-treat' analysis on the primary endpoint, NORRISK score, using the baseline observation carried forward.

Ethics

The Regional Committee for Medical Health Research Ethics, Norway, approved the study protocol on 30 May 2011 (ID: 2011/561a). Prior to inclusion, all patients received verbal and written information about the study and gave informed, written consent to participate.

Results

During the inclusion period 1498 patients were assessed for eligibility, whereof 701 (47%) were candidates for inclusion and randomly assigned to the IG (350 patients) or the CG (351 patients). The most common reason for not being eligible was a risk score below the inclusion threshold. After being randomly assigned, 30 patients dropped out of the IG as did 20 from the CG. Reasons for drop-outs

are shown in Figure 2. Another 15 patients in the IG and 35 patients in the CG were lost to follow-up whereof 2 patients died (both in the CG) and 48 were unreachable at 3-year follow-up. Finally, 601 patients (86%) remained in the follow-up study population, with 305 patients (87%) in the IG and 296 patients (84%) in the CG (Figure 2).

Baseline characteristics were quite similar between the groups (Table 1). The mean NORRISK scores differed only marginally at baseline (Table 2). The baseline and follow-up scores were moderately correlated ($r = 0.706$). The difference between the mean change scores indicated a risk reduction of 0.85% (95% CI: −1.46 to −0.25, $P = 0.006$) on intervention vs. usual care. When controlling for baseline imbalance using ANCOVA, the difference between the mean change scores of each treatment group was −0.92 (95% CI: −1.48 to −0.36, $P = 0.001$) which means that NORRISK score improved by an estimate of −0.92% on average in the IG compared to the CG. The statistical significance of this result improved when the scores were analyzed in their logged form ($P = 0.0001$). An R squared = 0.506 indicated that 51% of the variation in the NORRISK follow-up score was explained by the intervention and the baseline score, while 49% could be due to hidden confounders and chance.

An additional 'intention-to-treat' analysis, where the NORRISK score at follow-up was considered unchanged from baseline, in subjects who did not complete the trial (baseline observation carried forward) revealed similar results, with a difference in mean change in the IG compared to mean change in the CG of −0,73% (95% CI: −1.21 to −0.24, $P = 0.003$).

As shown in Table 2 results for the other cardiovascular risk scores considered, NORRISK 2, Framingham and PROCAM, showed a similar and significant beneficial efficacy of the intervention programme in lowering cardiovascular risk. SCORE2 was not included in the protocol, but post-hoc analysis showed a similar significant risk reduction (albeit with lower overall risk) as the other algorithms.

As regards secondary endpoints (Table 3), comparison between the two treatment groups showed no statistically significant difference between the mean change values adjusted for age and sex; SBP (−0.91, 95% CI: −3.01 to 1.20, $P = 0.398$), DBP (−0.26, 95% CI: −1.54 to 1.01, $P = 0.686$), TC (−0.13, 95% CI: −0.29 to 0.03, $P = 0.112$) and HDL-C (0.004, 95% CI: −0.03 to 0.04, $P = 0.811$) indicating no significant improvement in the IG compared to the CG. For LDL-C and TG, we found a borderline statistically significant difference between the mean change values adjusted for age and sex (−0.14, 95% CI: −0.28 to 0.01, $P = 0.063$) and (−0.12, 95% CI: −0.25 to 0.01, $P = 0.081$) respectively. The correlation between baseline and follow-up measurements was low for all endpoints ($r < 0.8$), except HDL-C, supporting the adequacy of using the ANCOVA approach to increase power. Analyzing the data in their logged form did not change the results for any of these endpoints; SBP, DBP, TC, HDL-C, LDL-C and TG when controlling for the confounding effect of age and sex. Data on HbA1c and waist circumference were not evaluated due to high proportion of missing values.

The records demonstrated that treatment with antihypertensives and lipid-lowering drugs were common in both groups and increased slightly during follow-up. Antihypertensive medication at baseline was given in 51.8 and 49.3% of patients in the IG and the CG, respectively, and increased to 57.4 and 57.1% at study end. Similarly, lipid-lowering drugs were given in 42.3% in the IG and 35.8% in the CG at baseline, increasing to 48.9 and 49.3% respectively, at 3 years.

The frequency of daily smokers and metabolic syndromes decreased between baseline and follow-up (Table 4). The relative decrease of daily smokers was 47% in the IG and 25% in the CG (chi-square = 8.9023, $P = 0.0028$). The relative decrease in metabolic syndromes was 19% in the IG and 3% in the CG (chi-square = 24.1740, $P < 0.0001$).

There were 25 cardiovascular events in the randomized population during follow-up (11 myocardial infarction, 5 cerebral insult, 6 PCI, 2 coronary bypass surgery, 1 pulmonary embolism) with 16 events in the CG and 9 in the IG. There were two deaths, both in the CG.

Discussion

The results of this open label, randomized, controlled trial showed that a multimodal primary prevention programme consisting of a central hospital-based evaluation and primary care follow-up was beneficial after 36 months. NORRISK score, estimating risk of CVD mortality, improved by an estimate of 0,92% on average in the IG compared to the CG, while NORRISK 2, Framingham and PROCAM score, estimating risk of CVD events, improved by an estimate of −0,95 to −2,22%.

There are only a limited number of studies in primary prevention that reports effects on risk scores.[23] However, our results were quite similar to findings by Gysan *et al.*[24] who reported a significant reduction both in ESC-SCORE and CVD events. This study examined employers in a large company with ESC-SCORE > 5%, where the intervention was a 15-week multimodal outpatient intervention programme.[24]

Regarding the secondary outcome measures, we observed no statistically significant improvements in SBP, DBP, TC or HDL-C between the IG and the CG. For LDL-C and TG there was a borderline statistically significant difference between groups.

The lack of impact on traditional major risk factors as cholesterol and blood pressure may seem disappointing, but is in line with findings from major lifestyle studies and meta-analyses assessing effects of lifestyle interventions.[23,25,26] These studies demonstrate small, but significant changes in SBP and TC after 6–12 months, but the benefits gradually attenuate over time, especially regarding TC.[23] Hence, we might not expect larger benefits after 36 months in our study.

The clinical relevance of a 0.92% decrease in estimated CVD risk of mortality or similarly a 0.95–2.24% decrease in risk of CVD events (Table 2) may be discussed. However, such a benefit can be regarded as valuable, given the premise that the observed change in the four risk scores examined would in fact translate into reduction in CVD events, as reported in the study by Gysan *et al.*[24] A risk reduction of a similar magnitude has been discussed in a recent paper regarding primary prevention with statins[27] on the basis of a Cochrane report from 2013.[28] With a baseline risk level of 10% for CVD events, the authors have calculated a number needed-to-treat (NNT) of 138 treated with statins for 5 years to prevent one death. The results from our study would, if extrapolated to 10 years, prevent 0,92 cardiovascular deaths per 100 treated for 10 years, corresponding to a NNT of 111 for 10 years, or approximately 222 needed to treat for 5 years.

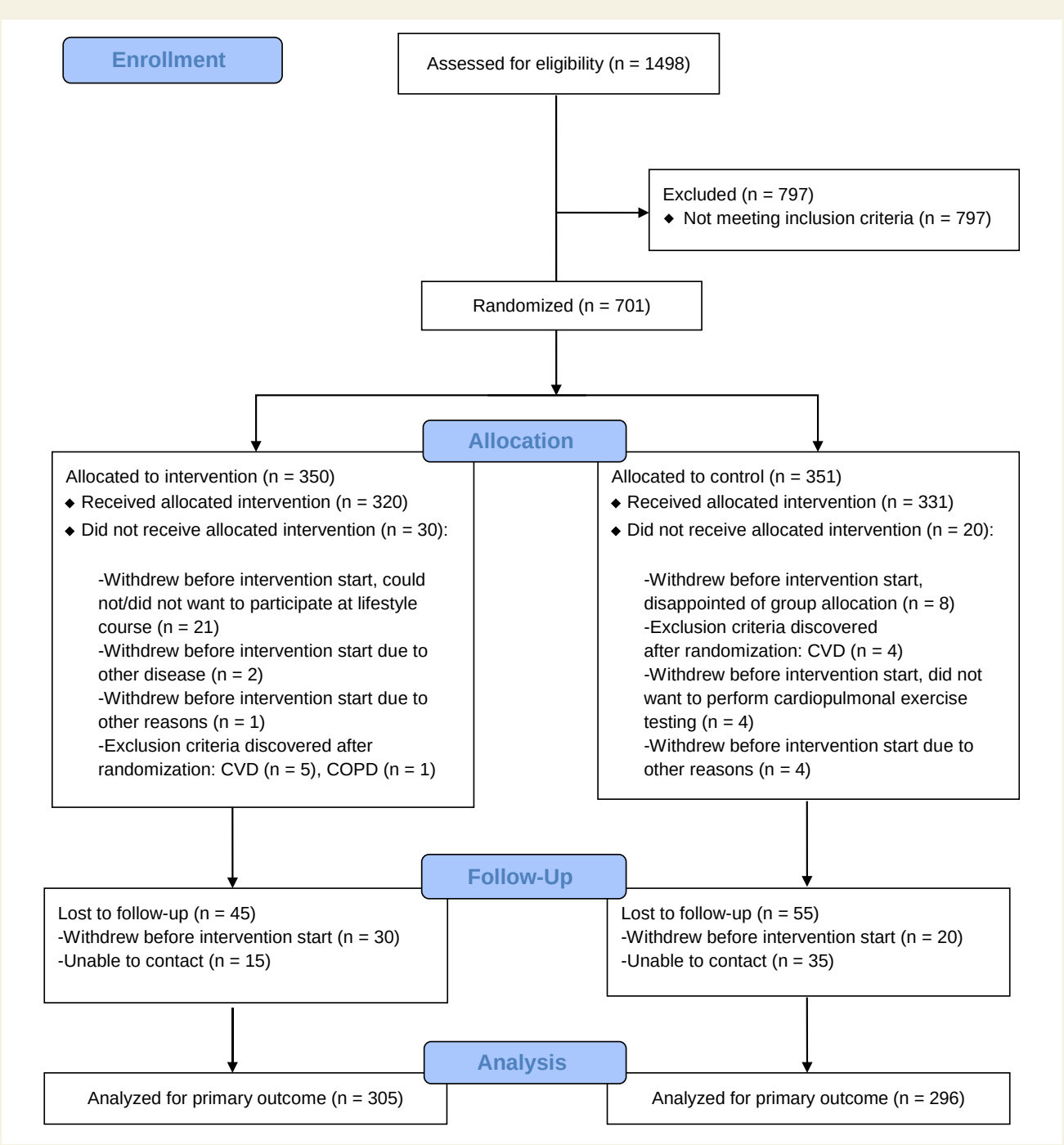


Figure 2 The CONSORT flow diagram. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

The value of any risk-reducing intervention will depend on the absolute baseline risk. In a paper evaluating statin-therapy in primary prevention, the authors reported beneficial cost-effectiveness when achieving a reduction in 10-year CVD risk from 7.5% to 5.6%.[29] Hence, a reduction of 0,92% (from 5,04%) in risk of cardiovascular mortality could similarly be regarded as clinically important as total event risk usually is two to three times higher than the risk of fatal CVD.[5]

The magnitude of the risk reduction is also comparable to that observed for potent drugs like for instance PCSK-9 inhibitors, as observed by Sabatine *et al.*[30] in the FOURIR-study. In this study they reported a reduction in the primary endpoint (CV-events) from 11.3% (placebo) to 9.8% (Evolocumab), corresponding to a hazard ratio of 0.85. To bring a different perspective, the NORRISK score declined slightly (from 5.04 to 4.92%) in the IG in spite of the fact that participants gained 3 years of age during the period, and considering that age has a major impact on cardiovascular risk level. The benefit of the intervention may hence be described as corresponding to eliminating the negative impact of turning three years older.

Table 1 Baseline demographic and clinical characteristics of patients analyzed for the primary outcome, and those lost to follow-up

	Patients analyzed		Patients lost to follow-up	
Baseline variables	**Intervention ($n = 305$)**	**Usual care ($n = 296$)**	**Intervention ($n = 45$)**	**Usual care ($n = 55$)**
Mean age (SD), years	53.7 (8.4)	54.4 (7.8)	53.1 (7.9)	50.8 (8.2)
Sex				
Female	109 (36%)	97 (33%)	21 (47%)	21 (38%)
Male	196 (64%)	199 (67%)	24 (53%)	34 (62%)
Employment				
Employed	208 (68%)	201 (68%)	30 (67%)	36 (66%)
Sick leave	16 (5%)	16 (5%)	2 (4%)	1 (2%)
Retired	22 (7%)	31 (10%)	0	3 (5%)
Disabled	44 (14%)	33 (11%)	7 (16%)	11 (20%)
Education level				
Primary school	47 (15%)	45 (15%)	12 (27%)	5 (9%)
High school	132 (43%)	114 (38%)	14 (31%)	21 (38%)
College	117 (38%)	126 (42%)	17 (16%)	26 (47%)
Smoking status				
Present	90 (30%)	76 (26%)	22 (49%)	19 (35%)
Previous	87 (29%)	87 (29%)	11 (24%)	13 (24%)
Metabolic syndrome	189 (62%)	166 (56%)	33 (73%)	42 (76%)
Diabetes mellitus	52 (17%)	64 (22%)	12 (27%)	4 (7%)
Mean blood pressure (SD)				
Systolic (mmHg)	138 (16)	138 (14)	134 (13)	140 (18)
Diastolic (mmHg)	85 (9)	85(10)	84 (9)	85 (11)
Mean blood values (SD)				
Total cholesterol (mmol/L)	5.51 (1.20)	5.38 (1.26)	5.79 (1.14)	5.65 (1.23)
LDL-cholesterol (mmol/L)	3.53 (1.10)	3.41 (1.10)	3.81 (1.08)	3.62 (1.03)
HDL-cholesterol (mmol/L)	1.28 (0.38)	1.27 (0.36)	1.27 (0.31)	1.33 (0.58)
Triglycerides (mmol/L)	1.88 (1.14)	1.74 (1.25)	2.35 (2.91)	2.21 (1.62)
Fasting blood glucose (mmol/l)	6.07 (1.68)	6.21 (1.90)	6.51 (2.27)	5.63 (0.80)
HbA1c (%)	5.95 (0.92)	6.08 (0.98)	6.22 (1.06)	5.72 (0.56)
Mean waist circumference (SD), cm	106 (14)	105 (13)	109 (17)	107 (13)
Cardiovascular medication				
Antihypertensive drugs	158 (52%)	146 (49%)	19 (42%)	19 (35%)
Lipid-lowering drugs	129 (42%)	106 (36%)	15 (33%)	16 (29%)
Mean NORRISK score (SD)	5.04 (5.85)	5.27 (5.02)	5.34 (6.51)	4.12 (4.36)

Data are *n* (%) or mean (SD) unless stated otherwise.
SD, standard deviation.

The costs of our intervention were minor, as follow-up in primary care was based on the existing health care service and primary prevention largely is a primary care task. Costs related to the initial in-hospital course, including digital follow-up and newsletters, were comparable to hospital-based cardiac rehabilitation costs in Norway, and would correspond to a cost of approximately 900 EUR.

Despite the lack of significant improvements in lipids and blood pressure, we found a significant reduction in NORRISK score and similar risk algorithms. Thus, the effect on NORRISK is likely to be related to other risk factors involved in the score.

The proportion of daily smokers in the study population was higher than the Norwegian average (IG 30%, CG 26%) and the proportion of patients who quit smoking was significantly greater in the IG than in the CG, explaining some of the reductions in NORRISK score.

There was also a high proportion with metabolic syndrome in the population and the proportion with metabolic syndrome was reduced from 62 to 50% in the IG compared to the CG, where the reduction was minimal (from 56 to 54%). Thus, as the presence of metabolic syndrome influences the NORRISK score, some of the NORRISK score reduction can be explained by this effect on metabolic factors.

While a more active and aggressive strategy for identifying and treating high cholesterol and blood pressure pharmacologically may be effective, and could be recommended in many parts of Europe, the present study shows that additional risk reduction may also be achieved by targeting other risk factors, i.e. smoking and metabolic syndrome. This may be especially important in younger individuals, as most risk algorithms will not identify and classify these persons

Table 2 Efficacy of the multimodal primary prevention intervention programme for reducing risk of developing cardiovascular disease as estimated by NORRISK, NORRISK 2, Framingham and PROCAM score in patients receiving intervention vs. usual care at baseline and follow-up after 3 years

	Intervention ($n = 305$) mean (SD)	Usual care ($n = 296$ mean (SD)	Difference between means (95% CI)	*P*-value
NORRISK score				
Baseline	5.04 (5.85)	5.27 (5.02)		
Follow-up	4.92 (4.70)	6.01 (5.14)		
Change	−0.11 (3.47)	0.74 (4.05)	−0.85 (−1.46 to −0.25)	0.006[a]
ANCOVA			−0.92 (−1.48 to −0.36)	0.001
NORRISK 2 score				
Baseline	8.17 (5.36)	7.99 (5.06)		
Follow-up	8.23 (5.59)	9.02 (5.99)		
Change	0.05 (3.68)	1.03 (3.56)	−0.97 (−1.55 to −0.39)	0.001[a]
ANCOVA			−0.95 (−1.52 to −0.38)	0.001
Framingham score				
Baseline	17.81 (10.51)	18.30 (11.77)		
Follow-up	15.98 (9.28)	18.53 (11.23)		
Change	−1.82 (8.23)	0.24 (8.63)	−2.06 (−3.41 to −0.70)	0.003[a]
ANCOVA			−2.24 (−2.43 to −1.04)	0.001
PROCAM score[b]				
Baseline	9.09 (8.46)	9.32 (9.55)		
Follow-up	8.33 (7.76)	9.99 (10.47)		
Change	−0.74 (7.62)	0.67 (8.59)	−1.41 (−2.73 to −0.09)	0.037[a]
ANCOVA			−1.50 (−2.70 to −0.30)	0.014

ANCOVA, analysis of covariance; CI; confidence interval; SD; standard deviation.
[a]Comparison between the two groups by Student *t*-test.
[b]Missing; intervention group 6 ($n = 296$) and control group 11 ($n = 285$).

as qualifying for primary prevention with drugs. A study in Greece of 200 consecutive patients with age < 45 years, admitted with myocardial infarction, demonstrated that none of these patients had a SCORE risk above 1% (i.e. far below the recommended threshold of 5% for medical intervention), while a large proportion; 51,5%, had metabolic syndrome, and 79% were smokers.[31] Hence, the present study suggests that a broad approach to CVD risk reduction may have the potential to address other important risk aspects than cholesterol and blood pressure management, and this being achieved with a programme that predominantly utilizes resources within primary care, and with modest costs to the society. These findings also confirm the importance of focusing on smoking cessation in the field of lifestyle-based preventive cardiology which is under-represented according to findings in the study by Manyangu *et al.*[32]

Strengths and limitations

Strengths of our study are the high number of participants and the long follow-up time. The results were consistent for all four risk algorithms and the inclusion rate can be considered high, as 47% of the screened population was found eligible. Further, despite the well-known lower CVD risk of females the female participation rate in our study cohort was fairly good (IG: 36%, CG: 33%), which is of importance for the generalizability of the obtained results.

A limitation of this study is the risk of attrition bias because approximately 14% of the participants either withdrew after randomization or were lost to follow-up. The majority of these individuals never received the intervention, and excluding them from the analysis may not have biased our results seriously.[33] Since participants who depart from randomized treatment are usually a non-random subset, the potential for bias cannot be excluded.[34] Comparing the distribution of baseline characteristics in individuals with and without complete follow-up data demonstrate no important difference for the primary outcome variable NORRISK score, but a slightly higher frequency of daily smokers and metabolic syndromes among drop-outs. This might indicate that more individuals with poor health were susceptible to leave the study. Moreover, the different attrition rates in the two arms could have biased our results in both directions.[35] Due to missing follow-up data, the results of an 'intention-to-treat' analysis may differ from the 'on treatment' analysis, and there are limitations with both analysis strategies. As we had a clear research hypothesis that the intervention programme would be beneficial in lowering cardiovascular risk, we found the most important evaluation was to consider the 'on treatment' approach.[36] In this situation, confounding bias cannot be excluded although we controlled for the confounding effect of age and sex in the analysis of the secondary endpoints. With respect to the primary endpoint, age and sex were already considered in the scores. Results from the modified 'intention-to-treat' analysis showed a numerically lower efficacy than the 'on treatment' analysis, but within the same range.

Table 3 Efficacy of the multimodal primary prevention intervention programme on established risk factors of cardiovascular disease in patients receiving intervention vs. usual care at baseline and follow-up after 3 years

	Mean (standard deviation)			
	Intervention ($n = 305$)	Usual care ($n = 296$)	Difference between means (95% CI)	*P*-value
Systolic blood pressure (mmHg)				
Baseline	138.22 (16.16)	137.65 (14.31)		
Follow-up	133.35 (13.36)	134.34 (14.44)		
Change	−4.87 (16.48)	−3.31 (17.78)	−1.56 (−4.31 to 1.18)	0.264[a]
ANCOVA			−1.15 (−3.27 to 0.97)	0.286
Adjusted for age and sex			−0.91 (−3.01 to 1.20)	0.398
Diastolic blood pressure (mmHg)				
Baseline	84.53 (9.29)	84.94 (9.99)		
Follow-up	81.45 (8.13)	81.87 (8.83)		
Change	−3.03 (10.13)	−3.07 (10.71)	−0.04 (−1.63 to 1.72)	0.958[a]
ANCOVA			−0.28 (−1.56 to 1.004)	0.673
Adjusted for age and sex			−0.26 (−1.54 to 1.012)	0.686
Total Cholesterol (mmol/L)				
Baseline	5.51 (1.20)	5.38 (1.26)		
Follow-up	5.04 (1.13)	5.10 (1.21)		
Change	−0.47 (1.15)	−0.28 (1.23)	−0.19 (−0.38 to 0.002)	0.053[a]
ANCOVA			−0.12 (−0.28 to 0.04)	0.148
Adjusted for age and sex			−0.13 (−0.29 to 0.03)	0.112
LDL (mmol/L)				
Baseline	3.53 (1.10)	3.41 (1.10)		
Follow-up	3.18 (1.04)	3.25 (1.10)		
Change	−0.35 (1.03)	−0.18 (1.05)	−1.18 (−0.35 to −0.01)	0.037[a]
ANCOVA			−0.13 (−0.27 to 0.02)	0.087
Adjusted for age and sex			−0.14 (−0.28 to 0.01)	0.063
HDL (mmol/L)				
Baseline	1.28 (0.38)	1.27 (0.36)		
Follow-up	1.30 (0.41)	1.29 (0.37)		
Change	0.03 (0.23)	0.02 (0.23)	0.002 (−0.04 to 0.04)	0.916[a]
ANCOVA			0.003 (−0.03 to 0.04)	0.865
Adjusted for age and sex			0.004 (−0.03 to 0.04)	0.811
Triglyceride (mmol/L)				
Baseline	1.88 (1.14)	1.74 (1.25)		
Follow-up	1.64 (0.88)	1.70 (1.01)		
Change	−0.23 (0.97)	−0.05 (1.17)	−0.18 (−0.36 to −0.01)	0.037[a]
ANCOVA			−0.11 (−0.24 to 0.02)	0.105
Adjusted for age and sex			−0.12 (−0.25 to 0.01)	0.081

ANCOVA; analysis of covariance.
[a]Comparison between the two groups by Student *t*-test.

Another limitation of this study is the open-label nature of the trial, which has the risk of causing both performance and detection bias. The knowledge about treatment allocation might have influenced both the patient's behaviour and health care providers who may have evaluated patients in the two groups differently. Even participation in a CG may have resulted in a more pronounced attention on CVD risk in patients and their GPs than in 'real life' usual care, which might dilute the intervention efficacy.

Complete blinding of NORRISK and PROCAM score assessor was impossible, but the other risk algorithms were calculated automatically, and the blood samples were analyzed by laboratory staff unaware of treatment allocation. With regard to blood pressure, awareness of treatment allocation could have affected the measurements. Most likely the potential misclassification of primary and secondary endpoints would be non-differential, and the observed efficacy of intervention expected to represent diluted, not inflated.[37]

People who were willing to participate were probably more than average motivated for lifestyle change. Hence, the positive changes we observed may not be easily extrapolated to subjects with the poorest lifestyle and with minimal motivation for changes.

A further limitation concerns the fact that the intervention is multifaceted and the relative efficacy of its components'

Table 4 Efficacy of the multimodal primary prevention intervention programme on the frequency of daily smoking and metabolic syndrome in patients receiving intervention vs. usual care at baseline and follow-up after 3 years

	Intervention $n = 305$	Usual care $n = 296$
Daily smokers		
Baseline	90 (29.5%)	76 (25.7%)
Follow-up	48 (15.7%)	57 (19.3%)
Metabolic syndrome[a]		
Baseline	189 (62%)	166 (56%)
Follow-up	153 (50%)	161 (54%)

[a]Criteria for clinical diagnosis of the metabolic syndrome: 3 of 5 criteria. (i) Triglycerides ≥ 1.7 mmol/L (150 mg/dL) or drug treatment for elevatoed triglycerides. (ii) Waist circumference ≥ 88 cm (females), ≥ 102 cm (males). (iii) HDL <1.3 mmol/L (50 mg/dL) (females), <1.0 mmoL/L (40 mg/dL) (males) or drug treatment for reduced HDL-C. (iv) Systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mmHg or antihypertenisve drug treatment when history of hypertension. (v) Fasting glucose ≥ 5.6 mmol/L (100 mg/dL) or drug treatment of elevated glucose.

contributions to the overall positive finding cannot be determined, which would be a topic of interest for further research.

Finally, a possible limitation of the study could be a biased use of cardiovascular drugs in the two groups. As stated under *Interventions* any adjustments were left to the GPs, and recommended to be prescribed according to current guidelines. The records demonstrated that both lipid-lowering and antihypertensive drugs use increased moderately in both groups during the course of the study, with very similar changes in antihypertensives in both groups, but somewhat larger increase in the proportion treated with lipid-lowering drugs in the CG. A more pronounced increase in lipid-lowering drugs in the CG could have diminished the effect of the study intervention on cholesterol levels somewhat, and correspondingly on total cardiovascular risk scores, albeit with limited influence.

Conclusion

In a group of subjects with elevated cardiovascular risk in Norway, a newly developed prevention programme, combining an initial hospital-based lifestyle course with follow-up in primary care, resulted in a significant reduction in cardiovascular risk scores after 36 months. This benefit appeared achievable through primary prevention intervention efforts, with improvements in metabolic syndrome characteristics and smoking habits as prominent contributors to the positive results. The costs of the intervention were limited, and similar efforts may be considered established on a regular basis in Norway and other countries with similar needs for improved cardiovascular prevention.

Author contribution

I.S., M.A., S.A., T.O.K., J.G., N.E.M., D.E.R., and H.B. contributed to the conception or design of the work. J.G., D.E.R., N.E.M., M.V., C.S., B.L., L.D., and H.B. contributed to the acquisition of data. I.S., M.A., T.O.K., S.A., J.G., and H.B. contributed to the analysis or interpretation of data for the work. H.B., T.O.K., and I.S. drafted the manuscript. H.B., T.O.K., I.S., M.A., and J.G. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article cannot be shared publicly, due to strict national regulations regarding the protection of personal data.

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