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Original Scientific Paper

Effectiveness of nonpharmacological secondary prevention of coronary heart disease

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Aim **To summarize the current evidence with regard to the effectiveness of nonpharmacological secondary prevention strategies of coronary heart disease (CHD) and to investigate the comparative effectiveness of interventions of different categories, specific intervention components and the effectiveness in patient subgroups.**

Methods **A structured search of databases and manual search were conducted. Clinical trials and meta-analyses published between January 2003 and September 2008 were included if they targeted adults with CHD, had a follow-up of at least 12 months, and reported mortality, cardiac events or quality of life. Two researchers assessed eligibility and methodological quality, in which appropriate, pooled effect estimates were calculated and tested in sensitivity analyses.**

Results **Of 4798 publications 43 met the inclusion criteria. Overall study quality was satisfactory, but only about half of the studies reported mortality. Follow-up duration varied between 12 and 120 months. Despite substantial heterogeneity, there was strong evidence of intervention effectiveness overall. The evidence for exercise and multimodal interventions was more conclusive for reducing mortality, whereas psychosocial interventions seemed to be more effective in improving the quality of life. Rigorous studies investigating dietary and smoking cessation interventions, specific intervention components and important patient subgroups, were scarce.**

Conclusion **Nonpharmacological secondary prevention is safe and effective, with exercise and multimodal interventions reducing mortality most substantially. There is a lack of studies concerning dietary and smoking cessation interventions. In addition, intervention effectiveness in patient subgroups and of intervention components could not be evaluated conclusively. Future research should investigate these issues in rigorous studies with appropriate follow-up duration to improve the current poor risk factor control of CHD patients.** ***Eur J Cardiovasc Prev Rehabil*** **17:688–700 © 2010 The European Society of Cardiology**

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Introduction

Coronary heart disease (CHD) is a common and potentially fatal disease with high lifetime prevalence. In terms of mortality it represents the most important disease in the group of all cardiovascular diseases, which, in turn, are responsible for most of the deaths in developing and in industrialized countries [1]. In Germany and most other European countries, cardiovascular diseases cause more than 40% of annual deaths.

Although there has been a steady decline in the age-adjusted mortality from CHD, the absolute number of incident cases and hospital admissions because of CHD is

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immense and there have been reports suggesting that the mortality decline observed over past decades might be at an end or even reverse in the near future [2–4].

The development of CHD is multicausal and is related to a variety of risk factors, many of them strongly influenced by individual behaviour, such as smoking, exercise, diet, diabetes mellitus, hypertension and hypercholesterolemia [5]. It has been suggested that modification of nine major and modifiable risk factors could reduce the burden of CHD by approximately 90% [6].

These risk factors, however, also strongly influence the prognosis of patients with established CHD. In addition to the well-established pharmacological management of patients with CHD, behavioural changes to modify these lifestyle factors in affected individuals are therefore recommended to form the basis of all secondary prevention strategies of CHD [5].

Despite these recommendations, the implementation of nonpharmacological secondary prevention strategies is frequently limited or participation is low. Further, it has been shown that many patients suffering from CHD do not meet the recommended treatment targets and especially, that appropriate and beneficial lifestyle changes are rarely achieved [7]. This was recently confirmed by results of the Euroaspire III study, which provided evidence that although the frequency of recommended medical management has improved since the first Euroaspire survey in 1995, lifestyle changes hardly did [8]. It further showed that risk factor control is still problematic in patients with established CHD [8]. This highlights the importance of appropriate and effective nonpharmacological secondary prevention strategies for patients with CHD.

Although there have been systematic reviews and meta-analyses investigating the effectiveness of cardiac secondary prevention programmes in the past, certain issues were not addressed or had yet to be investigated in more detail [9,10]. The aim of this systematic review was therefore to update earlier systematic reviews by summarizing the current evidence with regard to the effectiveness of nonpharmacological secondary prevention strategies and to investigate the comparative effectiveness of different intervention strategies. In addition, an attempt was made to investigate the effectiveness of specific intervention components and the effectiveness of interventions in relation to certain individual patient factors, such as the indication for secondary prevention, sex, comorbid conditions and socioeconomic status.

Methods

Relevant publications were identified through a structured search of more than 30 electronic databases, including Medline, Embase and the Cochrane Library, accessed through the German Institute of Medical Documentation and Information. In addition, a manual search of reference lists included in the articles identified as part of the structured database search, was conducted. To focus on current publications, the literature published in any language between January 2003 and August 2008 was also searched. The following selection criteria were applied:

1. Study type: randomized controlled trials (RCTs), non-randomized controlled trials (CCTs) and meta-analysis
2. Follow-up duration: at least 12 months, when a study was reported in multiple publications, the latest follow-up outcomes were considered
3. Outcome mortality, cardiac events, or quality of life (Qol)
4. Intervention categories: nonpharmacological secondary prevention interventions including exercise-based, dietary, smoking cessation or psychosocial interventions, and combinations of these categories
5. Language: English and German

Meta-analyses were included in our systematic review to also reflect the evidence published before 2003. For meta-analyses to be eligible for our systematic review they had to fulfill the same criteria as primary studies. Meta-analyses that only aimed to or only included observational studies were therefore not considered eligible.

The titles, abstracts and full texts of all identified studies were reviewed independently by two researchers and evaluated with regard to their methodological quality using standardised quality checklists used by the German Institute for Documentation and Information. In brief, for primary studies these checklists consider the following aspects: selection process of intervention and control participants, allocation method, comparability of intervention groups, consideration of relevant confounders, blinding (single/double), comparability of circumstances beyond the intervention, validity of outcome assessment, attrition rate/ differential attrition, description of statistical methods and intention to treat analysis. For meta-analyses checklists consider specification of objectives, comprehensiveness of search strategy, selection criteria, data extraction process, quality assessment, description of statistical methods/sensitivity analysis, presentation of study flow, assessment of heterogeneity and publication bias.

Depending on the risk of bias, the studies were subsequently rated according to the grading system developed by the Scottish Intercollegiate Guidelines Network Review Group [11] . Quality assessment of the included studies was conducted independently by two researchers. Data extraction was performed by one researcher and cross-checked by another. Disagreements between

researchers in any matter related to the study-selection process, quality assessment or data abstraction were resolved in discussion.

Interventions were categorized based on exercise, diet, smoking cessation, and psychosocial strategies predominantly, depending on the intervention's main components or as multimodal if programmes consisted of more than one main component. Psychosocial interventions include psychological intervention as defined in earlier systematic reviews [10] and interventions addressing psychosocial risk factors, such as stress, depression, anxiety and exhaustion, as long as they were not based on pharmacological interventions. It was further attempted to compare intervention strategies with regard to their delivery mode as hospital-based or home-based.

To evaluate the effectiveness, qualitative and quantitative synthesis of the study results was performed and based, if possible, on studies with a small-to-moderate risk of bias. Effectiveness compared with usual care (if stated in individual studies or if the alternative intervention was perceived as minimal, such as single advice or print information) or comparative effectiveness was investigated. Our meta-analysis included studies only if these reported suitable outcomes or effect measures. Odds ratios were calculated for dichotomous outcome measures. As part of the primary analysis, pooled effects of primary studies were subsequently estimated using a generic inverse variance method with random effects, as described in the *Cochrane Handbook for Systematic Reviews* using RevMan 5.0 [12,13]. Pooled effect estimates were calculated for reported outcomes of mortality and cardiac events within the follow-up period. Secondary analysis also included results of identified meta-analyses. The most appropriate meta-analysis for each intervention category was selected. If primary studies included in these meta-analyses and ours overlapped, we excluded the primary studies from this secondary analysis to avoid double counting. As different instruments were used to evaluate Qol, this outcome was summarized qualitatively only.

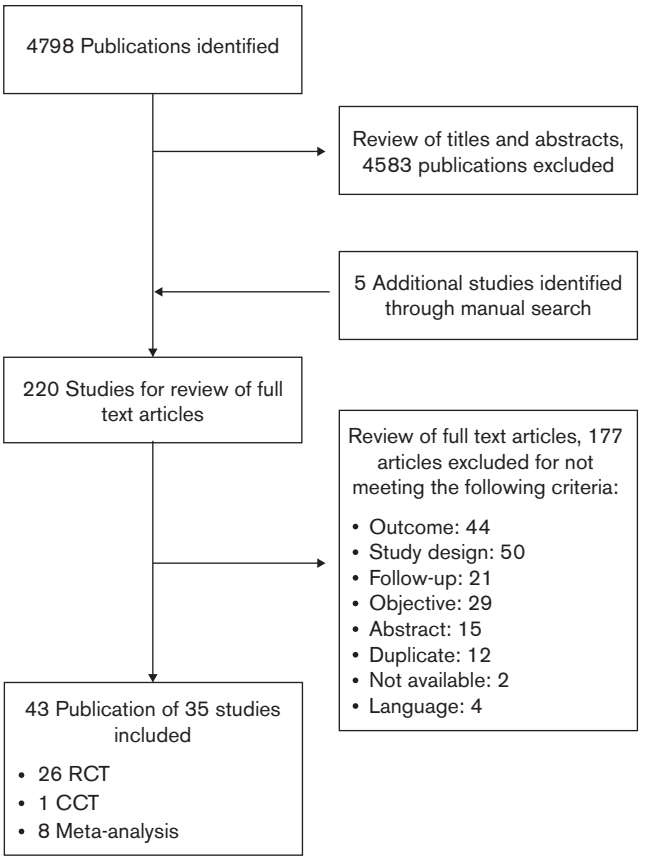
In sensitivity analyses we excluded outliers and calculated pooled estimates by using fixed effect models. In studies lacking suitable outcome data, it was attempted, whenever possible, to derive the number of patients with and without events from data given in these studies. To investigate the possibility of a publication bias, funnel-plot diagrams were constructed, including earlier calculated effect estimates and standard errors of identified studies with suitable outcome measures.

Results

Study selection

The literature search yielded 4798 citations. Of those, the selection process identified 43 medical publications reporting the results of 27 primary studies (26 RCTs and one CCT) and eight meta-analyses meeting the prespecified inclusion criteria (Fig. 1). Twenty-two studies were rated with good or high methodological quality (1 + + or 1 +) including seven meta-analyses. Multimodal secondary prevention programmes were investigated in 13 studies, 11 studies investigated exercise-based secondary prevention interventions, seven programmes focused on psychosocial interventions, whereas diet and smoking cessation interventions were each investigated in three studies. In addition, one meta-analysis compared home-based and hospital-based secondary prevention programmes. Only 18 studies reported, among others, mortality; 20 studies reported cardiac events and 24 studies reported Qol as an outcome parameter. The number of participants in primary studies varied between 87 and 3114 participants, including 12 studies with only approximately 200 or less participants. Similarly, there were marked differences in the duration and completeness of follow-up. Overall, follow-up was between 12 and 120 months, including 11 studies that followed patients for more than 24 months, and the follow-up completeness was between 61% and 100%. The studies that were included are illustrated in more detail in Tables 1 and 2.

Fig. 1



Flow-chart of study selection. CCT, nonrandomized controlled trials; RCT, randomized controlled trials.

Table 1 Characteristics of included primary studies (RCTs and CCTs) according to type of intervention

Reference	Comparison groups	Participants indication	Level of evidence	FU duration/ completeness	Mortality	Cardiac events	QoL
			Multimodal interventions				
Jolly *et al.* [14], UK	I: home-based C: in-hospital	I: 263 C: 262 MI/PCI	1++	24 I: 86%, C:88%	–	I: 20.1% C: 20.5% BGD: P=1	SF-36 BGD: NS
Briffa *et al.* [15], Australia	I: 6 wk CR C: lifestyle advise	I=57, C=56 MI/UAP	1++	12 I: 96%, C: 91%	I: 0% C: 3.6% BGD: NA	–	SF-36 BGD: significantly favouring Intervention 1/8 subscales (PFS)
Reid *et al.* [16], Canada	I: 33 sessions, 1 year C: 33 sessions, 3 months	I=196, C=196 CHD	1+	24 Overall: 64%	I: 2% C: 1% BGD: NA	I: 11.2% C: 11.2% BGD: NA	SF-36 BGD: NS
Young *et al.* [17], Canada	I: nurse case manager C: usual care	I=71, C75 MI	1+	I: 14, C: 15 (mean) 100%	I: 11.3% C: 14.7% BGD: $P>0.05$	I: 26 events C: 61 events BGD: IDR=1.59 (1.27–2.0; $P<0.001$)	BGD: significantly favouring Intervention 1/8 subscales (PFS)
Coull *et al.* [18], Scotland	I: 12 monthly sessions C: usual care	I=165, C=154 Elderly with CHD	1–	12 I: 90%, C: 90%	–	–	SF-36 BGD: significantly favouring Intervention 1/8 subscales (PFS)
Lisspers *et al.* [19], Sweden	I: 1 month in hospital and maintenance C: GP coordinated	I=46, C=41 PCI	1–	78 I: 60%, C: 63%	I: 2.2%[a] C: 14.6%[a] BGD: $P<0.04$	I: 30.4% C: 53.7% RR=0.57; $P<0.03$	–
Marchionni *et al.* [20], Italy	I1: 2 month in hospital I2: 2 month at home C: lifestyle advise	I1=90, I2=90, C= 90 MI	1–	14 I1: 87%, I2: 82%, C: 88%	–	–	Sickness impact profile: Some improvements in elderly patients compared with control
Munoz *et al.* [21], Spain	I: education of GPs C: usual care	I=515, C=468 MI/AP	1–	36 (median) I: 73%, C: 72%	I: 27% C: 27.6% BGD: HR=0.79 (0.47–1.34); $P=0.38$	I: 24% C: 23.5% BGD: HR=0.9 (0.56–1.45); $P=0.67$	BGD: NS
Murchie *et al.* [22], Scotland	I: prevention clinic, 1 year C: usual care	I=673, C=670 CHD	1–	56 (median) Overall: 98%	I: 14.9% C: 19.1% BGD: RR=0.78 (0.61–0.99); $P=0.038$	–	–
Yu *et al.* [23], Hong Kong	I: secondary prevention, 2 years C: usual care	I=181, C=88 Overweight with CHD	1–	24 I: 72%, C: 81%	I: 3% C: 5% BGD: $P>0.05$	–	SF-36 BGD: significantly favouring Intervention, 4/8 subscales
			Exercise-based interventions				
Hambrecht *et al.* [24], Germany	I: weekly supervised + home-based exercise C: PCI	Exercise=51, PCI=50 CHD	1++	12 100%	–	Exercise: 11.8% PCI: 30% BGD: OR=0.33 (0.12–0.9) 24 months: BGD: $P=0.039$	–
Arthur *et al.* [25], Canada	I: aerobic and resistance exercise C: aerobic exercise	I=46, C=46 Women postcardiac event	1+	18 I: 76%, C: 80%	–	–	SF-36 BGD:
Sandström *et al.* [26], Sweden	I: 3 months, control + supervised sessions C: advise and information material	I=50, C=51 Elderly with CHD	1+	12 100%	–	–	EuroQoL BGD: NS
Smith *et al.* [27], Canada	I: home-based C: hospital-based	I=120, C=122 CABG	1+	18 I: 80%, C: 83%	–	BGD: NS	SF-36 BGD: significantly favouring intervention, PCS and MCS
Arrigo *et al.* [28], Switzerland	I: diary + 3-monthly sessions C: usual care	I=129, C=132 Post-CR	1–	12 I: 81%, C: 93%	–	I: 16% C: 10% BGD: $P<0.01$	MacNew BGD: NS
Hage *et al.* [29], Sweden	I: supervised sessions, 6 months C: lifestyle advise	I=56, C=53 Elderly post-MI/ UAP	1–	53 (median) I: 78%, C: 83%	–	I: 21.4% C: 11.3%	EuroQoL BGD:NS

Table 1 (*continued*)

Reference	Comparison groups	Participants indication	Level of evidence	FU duration/ completeness	Mortality	Cardiac events	Qol
Hughes *et al.* [48], Scotland	I: exercise counselling and calls C: advise	I=35, C=35 Post-CR	1−	12 I: 94%, C: 94%	–	–	SF-36 BGD: NS
Bettencourt *et al.* [30], Portugal	I: 3 exercise sessions C: usual care	Overall=203 ACS	1−	12 Overall: 62%	–	–	SF-36 BGD: significantly favouring intervention, PCS and MCS
			Psychosocial interventions				
Berkman *et al.* [31], USA	I: behavioural therapy, 9 months C: information material	I=1238, C=1243 MI+depression/ dysthymia/social isolation	1++	29 (median) I: 79%, C: 79% (at 6 months)	–	I: 24.4% C: 24.1% BGD: HR=1.01 (0.86–1.18)	–
Appels *et al.* [32], Netherlands	I: group sessions, relaxation therapy C: usual care	I=366, C=344 PCI	1+	24–26 100%	–	I: 22% C: 20% BGD: HR=1.14 (0.81–1.6)	MacNew BGD: NS
Michalsen *et al.* [33], Germany	I: stress management C: written advise	I=52, C=56 CHD	1+	12 I: 92%, C: 98%	–	I: 4.2% C: 9.4% BGD: NA	SF-36 BGD: significantly favouring intervention, PCS
Karlsson *et al.* [34], Sweden	I: stress management+usual care C: usual care	I=111, C=113	1−	12 I: 97%, C: 91%	–		Cantril ladder of life BGD: significantly favouring Intervention
			Dietary interventions				
Burr *et al.* [35], Wales	Fish: fish oil Fruit: advise to eat fruits Fishfruit: both C: advise to eat healthy	Fish=764 Fruit=779 Fishfruit =807 C=764 Men with AP	1+	36–108	Fish oil: 18.5% Fruit: 17.1% Fish +fruit: 17.6% C: 14.3% BGD: NA	–	–
Tuttle *et al.* [36], USA	I: Dietary counselling C: advise according to guidelines	Lowfat=50 Mediterranean=51 C=101 MI	2+[a]	46 (median) Low fat: 100% Mediterranean: 98% C: 100%	Low fat: 0% Mediterranean: 0% C: 6.9% BGD (diet vs. C): $P=0.014$	MI Low fat: 6% Mediterranean: 2% C: 7.9% BGD (diet vs. C): $P=0.37$ UAP Low fat: 8% Mediterranean: 7.8% C: 20% BGD (diet vs. C): $P=0.024$	–
			Smoking cessation interventions				
Joseph *et al.* [37], USA	I: cessation counselling, 18 months C: counselling once	I=78, C=74 CHD[b]	1+	18 64–68%	–	I: 2.7% C: 7.7% BGD: $P=0.278$	Ferrans and Powers Index BGD: NS
Mohiuddin *et al.* [38], USA	I: cessation counselling C: cessation advise once	I=109, C=100 CHD[b]	1+	24 I: 95%, C: 96%	–	I: 18,3% C: 37% BGD: NA	–
Quist-Paulsen [39], Norway	I: information, nurse contact C: usual care	I=118, C=122 CHD[b]	2+[a]	12 I: 84%, C: 96%	–	–	CAST QoL questionnaire BGD: NS

ACS, acute coronary syndrome; AP, angina pectoris; BGD, between group difference; C, control; CABG, coronary artery bypass graft; CCT, nonrandomized controlled trial; CHD, coronary heart disease; CR, cardiac rehabilitation; GP, general practitioner; HR, hazard ratio; I, intervention; IDR, incidence density ratio; MCS, mental component score; MI, myocardial infarction; M, month; NA, not available; NS, not significant; OR, odds ratio; PCI, percutaneous coronary intervention; PCS, physical component score; PFS, physical functioning scale; Qol, quality of life; RCT, randomized controlled trial; RR, relative risk; SF, short-form 36 health survey; UAP, unstable angina pectoris; wk, week; yr, year. [a]Cardiac mortality. [b]smoker with CHD.

Effectiveness of secondary prevention programmes compared with usual care

Although the reported effectiveness of prevention programmes showed considerable heterogeneity, the majority of studies reported positive intervention effects related to mortality, cardiac events and Qol compared with usual care. In studies rated 1+ or 1++, absolute reductions in mortality and cardiac events were as high as 3.6 and 18.7%, respectively. However, many primary studies were not able to detect statistically significant reductions in mortality. In turn, only two methodologically less rigorous studies observed a significant increase in cardiac events associated with nonpharmacological secondary prevention strategies. Furthermore, the

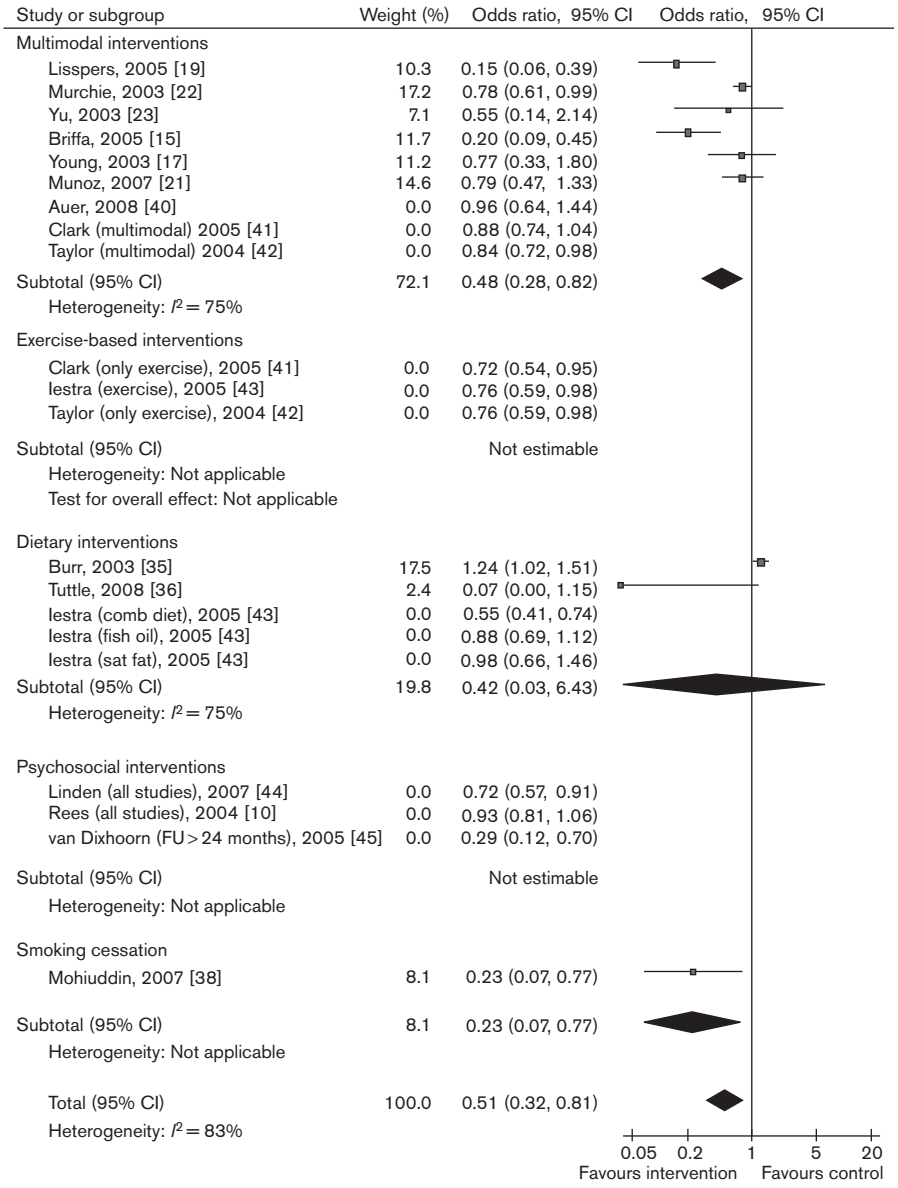
Table 2 Characteristics and main relevant outcomes of included meta-analyses (indication CHD refers to acute states, such as ACS, MI, PCI, CABG and a clinical diagnosis of CHD)

Referencer	Intervention categories	Studies indication	Level of evidence	FU duration	Mortality	Cardiac events	Qol
Auer *et al.* [40]	Multimodal (in-hospital)	*N*=26 ACS	1++	1–24	RR=0.96 (0.64–1.44)	RR=0.51 (0.23–1.13)	–
Clark *et al.* [41]	Multimodal, exercise	*N*=63 CHD	1++	0.75–60	All studies: RR=0.85 (0.77–0.94) Multimodal+exercise: RR=0.88 (0.74–1.04) Exercise only: RR=0.72 (0.54–0.95) No exercise: RR=0.87 (0.76–0.99) With FU 12 months: RR=0.97 (0.82–1.14) With FU 24 months: RR=0.52 (0.35–0.81) With FU>60 months: RR=0.77 (0.63–0.93)	All studies: RR=0.83 (0.74–0.94) Multimodal+exercise: RR=0.62 (0.44–0.87) Exercise only: RR=0.76 (0.57–1.01) No exercise: RR=0.86 (0.72–1.03)	–
Taylor *et al.* [42]	Multimodal, exercise	*N*=48 CHD	1+	6–72	All studies OR=0.80 (0.68–0.93) Multimodal: OR=0.84 (0.72–0.99) Exercise only: OR=0.76 (0.59–0.98) FU>12 months, OR=0.80 (0.69–0.92) Stratified according to indication: MI OR=0.81 (0.70–0.93) Other OR=0.92 (0.57–1.51)	All studies MI: OR=0.79 (0.57–1.09) CABG: OR=0.87 (0.65–1.16) PCI: OR=0.81 (0.49–1.34)	Two of 12 studies found improvement
Iestra *et al.* [43]	Multimodal, exercise, diet	*N*=22 CHD	1–	6–156	Exercise: RR=0.76 (0.59–0.98) Reduce sat. fatty acids: RR=0.98 (0.81–1.81) Fish oil: RR=0.88 (0.69–1.11) Combined diet: RR=0.55 (0.41–0.74)	–	–
Linden *et al.* [44]	Psychosocial	*N*=43 Cardiac events	1++	0.0772	All studies: OR=0.72 (0.59–0.94) FU>24 months: OR=0.89 (0.69–1.14)	All studies: OR=0.84 (0.7–1.02) FU24 months: OR=0.57 (0.37–0.86)	13 studies report Qol: significant improment through intervention
Rees *et al.* [10]	Psychosocial	*N*=36 CHD	1++	–	All studies: OR=0.93 (0.81–1.06) Stress management: OR=0.88 (0.67–1.15)[a]	All studies Non-deadly MI: OR=0.78 (0.67–0.9) Stress management: OR=0.69 (0.52–0.92)[a] Revascularization: OR=0.9 (0.78–1.02) Stress management OR=0.82 (0.42–1.62)[a]	Two of five studies reported improvement in Qol
Van Dixhoorn, [45]	Psychosocial (relaxation)	*N*=27 Cardiac event	1+	–	FU24 months: OR=0.29 (0.12–0.7)	All studies: OR=0.39 (0.27–0.57)	–
Jolly *et al.* [46]	Home vs. control Home vs. center	*N*=18 *N*=6 CHD (any)	1++	6 weeks to 4 years	RR= 1.39 (0.98–1.97), 6 studies RR= 1.15 (0.47–2.82), 1 study	–	Some improvements Improved PCS in home-based, 1 study

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PCS, physical component score; Qol, quality of life; RR, relative risk. [a]With versus without stress management.

majority of identified meta-analyses observed improvements in mortality and cardiac events associated with nonpharmacological secondary prevention strategies, with relative risk reductions of about 20% in most cases (Table 2). These findings are consistent with our meta-analyses of primary studies, which found overall significant reductions in mortality [0.51 (0.32, 0.81)] and borderline significant reductions in cardiac events [0.79 (0.58, 1.08)] as presented in Figs 2 and 3 and Table 3. If earlier identified meta-analyses were included without leading towards double counting of studies (Auer *et al.* [40] concerning multimodal, Iestra *et al.* [43] concerning exercise and diet, and Van Dixhoorn *et al.* [45] concerning psychosocial interventions), the evidence of intervention effectiveness was even more conclusive (Table 3).

Fig. 2



Primary meta-analysis of studies reporting mortality according to intervention category. Only primary studies were included in pooled estimates. CI, confidence interval.

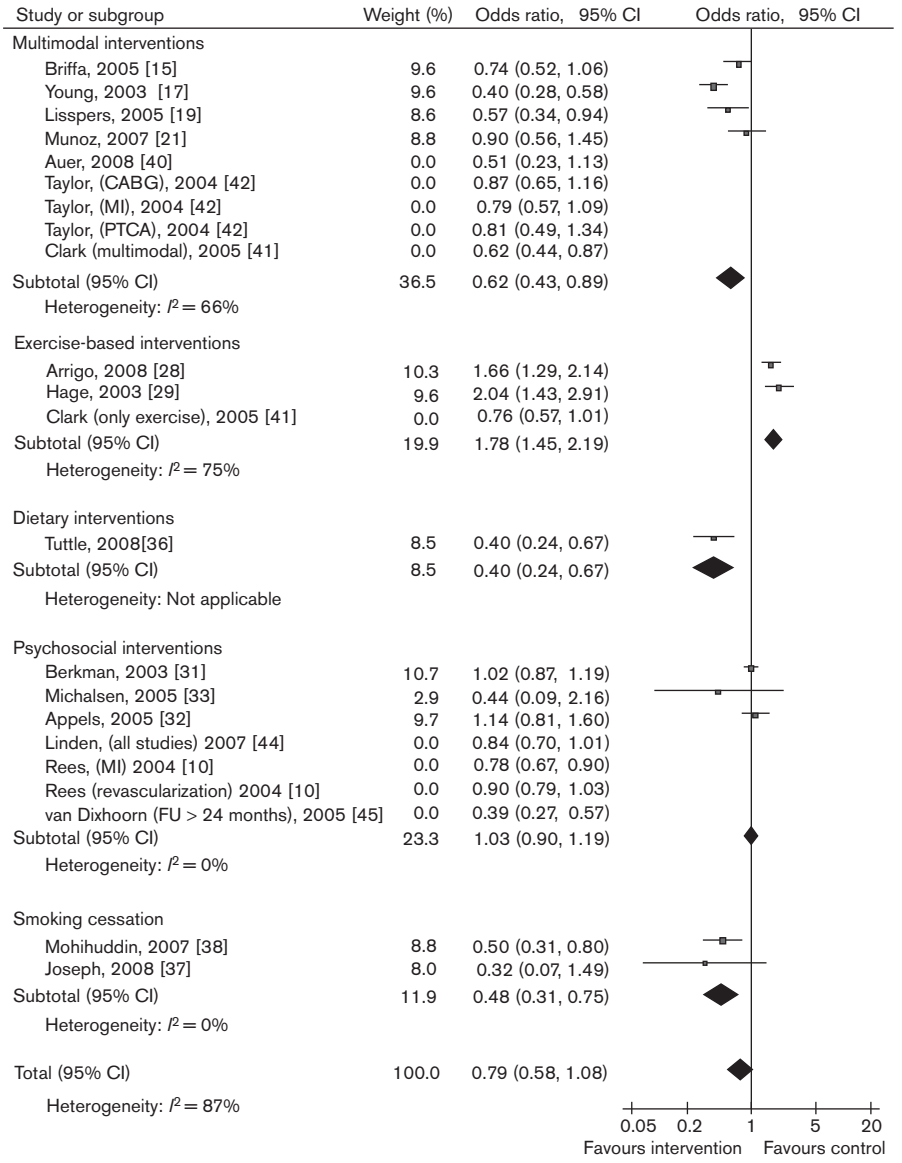
Multimodal interventions

Five methodologically rigorous studies investigated the effectiveness of multimodal interventions compared with no intervention control or usual care groups. Of three meta-analyses [40–42], two reported [41,42] a significant reduction in mortality. The remaining meta-analysis and both RCTs [15,17] reported a trend towards improved mortality. Of three meta-analyses and one RCT that reported cardiac events, two studies [17,41] found a significant reduction associated with the intervention. Only two methodologically rigorous studies investigated Qol, the meta-analyses by Taylor *et al.* [42] and the RCT by Briffa *et al.* [15]. Both reported only some improvements in Qol associated with the intervention, and two of three methodologically less rigorous studies found an improvement in at least one Qol subscale [18,23]. Observed reductions in mortality and cardiac events were more conclusive in meta-analysis as is illustrated in Figs 2 and 3, and Table 3. Findings were also robust to sensitivity analyses.

Exercise-based interventions

Of the three studies rated 1+ or 1++ investigating the effectiveness of exercise-based interventions

Fig. 3



Primary meta-analysis of studies reporting cardiac events according to intervention category. Only primary studies were included in pooled estimates. CI, confidence interval.

compared with usual care, two meta-analyses reported mortality. They found a significant reduction in mortality associated with exercise-based interventions. Similarly, one of these studies [41] reported cardiac events and found a significant reduction in events associated with the interventions. One further methodologically less rigorous meta-analysis confirmed these findings [43]. In contrast, the only two primary studies reporting cardiac events [28,29] observed increased event rates associated with exercise training, which resulted in a similar finding in our meta-analysis (Figs 2 and 3 and Table 3). The studies were of lower methodological quality, however. With regard to mortality, the only three studies suitable for meta-analysis were themselves meta-analyses and partly included identical primary studies. Hence, pooled estimates were not calculated as part of primary analysis.

Psychosocial interventions

Three of six studies rated 1 + or 1 + + investigated the effect of psychosocial interventions on mortality, and all of them were meta-analyses. Although two reported a significant reduction in mortality [44,45], the remaining study found only a trend towards improved mortality [10]. Of these six studies all three meta-analyses also reported significant reductions in the frequency of cardiac events.

Table 3 Results of primary and secondary meta-analyses: pooled effect estimates as odds ratios with 95% confidence intervals and numbers of comparisons included in meta-analysis (*italic: I^2 >50%*)

Analysis	Mortality	Cardiac events
	Overall	
Primary studies	*0.51 (0.32, 0.81)*	*0.79 (0.58, 1.08)*
Number of comparisons	9	12
Including one MA each category	*0.58 (0.43, 0.78)*	*0.73 (0.55, 0.97)*
Number of comparisons	13	15
	Multimodal	
Primary studies	*0.48 (0.28, 0.82)*	*0.62 (0.43, 0.89)*
Number of comparisons	6	4
Including one MA	*0.71 (0.60, 0.85)*	*0.60 (0.44, 0.83)*
Number of comparisons	7	5
	Exercise-based	
Primary studies	–	1.78 (1.45, 2.19)
Number of comparisons	0	2
Including one MA	0.76 (0.59, 0.98)	*1.36 (0.76, 2.44)*
Number of comparisons	1	3
	Dietary	
Primary studies	*0.42 (0.03, 6.43)*	0.40 (0.24, 0.67)
Number of comparisons	2	1
Including one MA	*0.70 (0.31, 1.56)*	0.4 (0.24, 0.67)
Number of comparisons	3	1
	Psychosocial	
Primary studies	–	1.03 (0.90, 1.19)
Number of comparisons	0	3
Including one MA	0.29 (0.12, 0.70)	*0.74 (0.44, 1.26)*
Number of comparisons	1	4
	Smoking cessation	
Primary studies	0.23 (0.07, 0.77)	0.48 (0.31, 0.75)
Number of comparisons	1	2
Including one MA	0.23 (0.07, 0.77)	0.48 (0.31, 0.75)
Number of comparisons	1	2
	Indication for secondary prevention	
ACS, PCI or CABG	*0.47 (0.24, 0.92)*	Not estimated
	7	
CHD	0.55 (0.27, 1.14)	Not estimated
	3	

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHD, coronary heart disease; MA, meta-analysis; PCI, percutaneous coronary intervention.

In contrast, the three remaining RCTs were not able to find a significant intervention effect. Again, with regard to mortality, the only three studies suitable for meta-analysis were themselves meta-analyses and pooled estimates, and therefore, were not calculated. However, our meta-analysis did not find an intervention effect related to cardiac events and thereby confirmed qualitative data synthesis (Table 3). Of the four methodologically rigorous studies investigating Qol, the two RCTs [33,47] report a significant improvement associated with the intervention, whereas one of the meta-analyses reported a significant positive intervention effect [44].

Dietary interventions

One less rigorous meta-analysis [43] investigated the mortality of patients associated with dietary interventions and reported a significant mortality reduction associated with a combined dietary intervention but not with a reduction in saturated fatty acids alone. Of two further studies (one RCT and one CCT) the CCT reported a significant mortality reduction by a Mediterranean and a low-fat diet compared with usual care [36], whereas the other study observed a trend towards lower mortality rates in a dietary advice control group compared with groups advised to take fish oil, fruits or fish oil and fruits, respectively. Tuttle *et al.* [36] also observed a significant reduction in the frequency of unstable angina but not myocardial infarctions in the low-fat and Mediterranean diet groups compared with control groups. Cardiac events were not investigated in both the other studies and Qol was not investigated in any of the included studies. As part of our meta-analysis, different intervention groups of included studies were combined. Meta-analyses showed no significant reduction in mortality and only one study was available to calculate the pooled estimates related to cardiac events (Figs 2 and 3, and Table 3).

Smoking cessation

The only study that compared a smoking cessation programme with usual care and investigated mortality reported significant improvements associated with the intervention [38]. In addition, this and one other study presented a trend towards reduced cardiac event rates, without reporting significance levels. Two studies investigated Qol and found no significant improvements associated with the intervention. On the basis of these studies, the meta-analysis found significant reductions in mortality [odds ratio, 0.23 (0.07, 0.77)] and cardiac events [odds ratio, 0.48 (0.31, 0.75)].

Comparative intervention effectiveness

Only nine methodologically rigorous studies directly compared different intervention strategies.

Interventions of different categories

Two high-quality meta-analyses [41,42] compared interventions of different categories, as defined in our analysis, namely multimodal strategies, with and without exercise components and purely exercise-based interventions. Their findings indicate that the inclusion of an exercise component is associated with a greater reduction in mortality than programmes without exercise component.

Different dietary strategies

In three studies [35,36,43] that compared different dietary interventions, Iestra *et al.* [43] observed more substantial effects through combined dietary changes (increase in fibres, fish and unsaturated fatty acids) than through low, saturated fat diets alone, and Burr *et al.* [35] and Tuttle *et al.* [36] report no difference between low-fat versus Mediterranean and fish oil versus fruit versus fish oil and fruit diets, respectively.

Psychological interventions including stress management

Only one high-quality meta-analysis compared different psychological interventions and found significantly improved

outcomes associated with studies that included a stress management programme compared with those without stress management programmes [10].

Home versus hospital-based

One high-quality meta-analysis found no difference between home-based and hospital-based interventions [46]. Three RCTs also compared home-based and hospital-based intervention strategies. One study, rated 1 + +, indicated no difference between both the strategies in terms of cardiac events and Qol. The other study by Smith *et al.* [27] found an increase in Qol in those who participated in home-based secondary prevention strategies but no difference in cardiac events. The remaining less rigorous study by Marchionni *et al.* [20] reported some improvement in Qol in the home-based group.

Duration/extent of intervention

No study specifically compared intervention strategies of different intensities or duration. Only Reid *et al.* [16] compared a secondary prevention programme with a duration of 3 months to an extended programme over 12 months but for the same number of intervention sessions. No differences in mortality, cardiac events and Qol were reported by the investigators.

In addition, two exercise-based studies compared either aerobic versus aerobic and resistance training [25], or percutaneous coronary intervention (PCI) versus supervised exercise [24] interventions, respectively. Whereas the high-quality study by Hambrecht *et al.* [24] reported superiority of exercise over PCI, Arthur *et al.* [25] indicated only some improvements in Qol of the aerobic and resistance group.

Effectiveness of interventions according to participant characteristics

Studies have rarely investigated effectiveness according to participant characteristics.

Indication for secondary prevention

Fifteen primary studies and one meta-analysis [14,15,17,19–21,25,27–32,34–36,45] investigated intervention effectiveness in patients with acute coronary syndrome, PCI or coronary artery bypass graft, respectively, and 13 studies compared with usual care. In contrast, 12 primary studies included patients with any diagnosis of CHD [16,18,22–24,26,28,33,37–39,48], 12 studies compared effectiveness with usual care. Studies that included more acute patients as identified by acute coronary syndrome, PCI or coronary artery bypass graft more frequently reported favourable intervention effects as presented in Table 1 and partly confirmed by meta-analysis (Table 3).

Patient age and sex

In most studies, the mean age of study participants was between 50 and 65 years and only three methodologically less rigorous studies specifically included participants of distinct age groups, in all cases including elderly patients [18,26,29]. With regard to the sex of the participants, approximately three-quarters of the participants were men and only two studies focused on either men [35] or women [25]. It was, therefore, not possible to investigate age or sex as a modifying factor conclusively.

Discussion

To our knowledge this systematic review and meta-analysis is the first that aimed to summarize the evidence with regard to all major nonpharmacological secondary prevention strategies for patients with CHD. In summary, it provides conclusive evidence for the effectiveness of nonpharmacological secondary prevention strategies compared with usual care. In evaluating the interventions of different categories there seems to be more consistent evidence for the effectiveness of multimodal and exercise-based interventions concerning mortality and for psychosocial interventions concerning Qol. With regard to specific intervention characteristics, included studies provided evidence that home-based and hospital-based strategies do not seem to differ in their effectiveness, although indicating somewhat better Qol in home-based patients. Further, stress management programmes as part of psychosocial interventions were found to be particularly effective in one meta-analysis. In addition, one study provided evidence for the superiority of supervised exercise training compared with PCI in patients with stable CHD. Apart from that, the studies were not able to provide conclusive evidence about the effectiveness of specific intervention components, such as different exercise strategies, combinations within the multimodal secondary prevention strategies or most effective psychosocial and smoking cessation interventions.

This systematic review thereby strengthens the evidence from earlier meta-analyses regarding the effectiveness of exercise-based and multimodal interventions. With this regard, for example, the earlier systematic review by Jolliffe *et al.* [9] reported similar effectiveness to that observed in our review. It does, however, add important information beyond that of earlier research because it not only focuses on one nonpharmacological secondary prevention category, but also gives a comprehensive update of the evidence with regard to all major nonpharmacological secondary prevention strategies for patients with CHD. For example, these findings indicate somewhat conflicting findings of a recent Cochrane review of psychological interventions by Rees *et al.* [10], which is included in our systematic review, and two other included meta-analyses investigating the effectiveness of psychological interventions [44,45]. This systematic review further provides some evidence that exercise-based and psychosocial interventions seem to be associated with improvements in different relevant outcome parameters, mortality and

Qol, which could have implications for future secondary prevention programmes. Dietary strategies form an important part of secondary prevention since publication of the Lyon Heart Study [49] and the association between dietary factors and CHD has been investigated extensively in the past [50]. However, only two primary studies and one meta-analysis with less rigorous methodology were identified within this review. Despite the advancing knowledge about the impact of traditional and newer dietary factors on the development and progression of CHD, our review highlights that the evidence with regard to most effective dietary interventions for patients with established disease is limited considerably. Similarly, recently published meta-analyses of behavioural smoking cessation interventions found that intensive behavioural and psychosocial strategies can effectively increase abstinence in those motivated to quit smoking [51,52]. Although their findings support the evidence of effectiveness of nonpharmacological smoking cessation programmes, clinical outcomes relevant to cardiac patients were not considered in these studies. This question was addressed by Critchley and Capewell. [53] who investigated the impact of smoking cessation in patients with CHD and found substantial reductions in mortality. Their findings, however, could not be conclusively substantiated in this systematic review. In contrast to our systematic review, the meta-analysis by Critchley and Capewell was not based on RCTs testing intervention effectiveness but on data from observational studies comparing the outcome of those who quit and those who did not quit smoking. Any conclusions with regard to the effectiveness of smoking cessation interventions in relation to mortality, cardiac events or improved Qol are therefore speculative.

This review thereby indicates that the evidence base with regard to the effectiveness of two of the best-known contributors to the prognosis of CHD patients, dietary factors and smoking status, is relatively weak compared with that of other intervention strategies. Especially in the light of recent findings from the Euroaspire III study, this should be cause for concern. Findings of that study confirmed that in patients with established CHD, overweight and obesity have increased dramatically since the first Euroaspire study in 1995. Furthermore, it showed that smoking rates among cardiac patients did not change in recent years [8]. Hence, there is great need for a stronger evidence base and more effective dietary and smoking cessation interventions for patients with CHD.

As with any systematic review, some limitations of our study should be noted. First, publication bias needs to be addressed. Although we aimed to conduct a highly comprehensive review of the literature and performed manual searches of identified reference lists, there was some indication of a publication bias in funnel-plot diagrams (not presented here), which suggests a potential risk of overlooked studies. Second, we had to restrict the inclusion of studies to the time since 2003, which naturally does not allow the identification of earlier published studies. However, our systematic review was also aimed at including meta-analyses published since 2003 to include not only current but also earlier evidence of nonpharmacological secondary prevention programmes. Third, the estimation of pooled estimates through meta-analysis was frequently restricted to only few included studies. This, however, was the result of inappropriate presentation of findings by some studies or a general lack of appropriate studies to answer investigated research questions. In addition, there was a marked heterogeneity in most pooled effect estimates, which limits their reliability further. Fourth, the investigation of specific effective intervention components and of important patient characteristics influencing effectiveness was very limited. Similarly, it was not possible to conclusively evaluate the effectiveness of interventions in those who are commonly under-represented in clinical trials, such as women, socially deprived patients or ethnic minorities. This, however, was also caused by a lack of suitable studies investigating these questions and should be part of future research.

In conclusion, there is consistent evidence of the effectiveness of exercise-based and multimodal interventions with regard to mortality and cardiac events. Further, there is some evidence for the effectiveness of psychosocial interventions with regard to improvements in Qol. In addition, our findings indicate that home-based and hospital-based interventions are equally effective at potentially lower costs of home-based interventions. In contrast, the identification of intervention components or patient characteristics, which are associated with improved outcomes, was limited. At present it is therefore not possible to recommend specific and most effective intervention components or subgroups of patients who will benefit, in particular. Furthermore, evidence of effectiveness of dietary and smoking cessation interventions in relation to important outcome measures is limited. Within the context of still inadequate lifestyle changes of patients with CHD, as indicated in recent representative studies, further research to investigate dietary and smoking cessation interventions, specific intervention components and important patient subgroups in methodologically rigorous RCTs with suitable follow-up duration is warranted.

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