Clinical research study implementation of case-finding strategies for heart failure and chronic obstructive pulmonary disease in the elderly with reduced exercise tolerance or dyspnea: A cluster randomized trial

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Background Heart failure (HF) and chronic obstructive pulmonary disease (COPD) often remain undiagnosed in older individuals, although both disorders inhibit functionality and impair health. The aim of the study was to assess the effectiveness of a case-finding strategy of these disorders.

Methods This is a clustered randomized trial; 18 general practices from the vicinity of Utrecht, the Netherlands, were randomly allocated to a case-finding strategy or usual care. Multimorbid community subjects (≥65 years) with dyspnea or reduced exercise tolerance were eligible for inclusion. The case-finding strategy consisted of history taking, physical examination, blood tests, electrocardiography, spirometry, and echocardiography. Subsequent treatment decisions were at the discretion of the general practitioner. Questionnaires regarding health status and functionality were filled out at baseline and after 6 months of follow-up. Information regarding changes in medication and health care use during the 6 months follow-up was extracted.

Results A total of 829 participants were randomized: 389 in the case-finding strategy group and 440 in the usual care group. More patients in the case-finding group received a new diagnosis of HF or COPD than the usual care group (cumulative incidence 34% vs 2% and 17% vs. 2%, respectively). Scores for health status, functionality, and health care use were similar between the 2 strategies after 6 months of follow-up.

Conclusions A case-finding strategy applied in primary care to multimorbid older people with dyspnea or reduced exercise tolerance resulted in a number of new diagnoses of HF and COPD but did not result in short-term improvement of health status compared to usual care. (Am Heart J 2020;220:73-81.)

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Dyspnea and reduced exercise tolerance are highly common in older people, with prevalence rates varying between 20% and 60%.[1,2] In older populations, especially those with multimorbidity and/or polypharmacy, it is difficult to distinguish between disorders that could underlie these complaints and physical deconditioning related to aging. As a result, the major causes for these complaints, that is, heart failure (HF) and chronic obstructive pulmonary disease (COPD), often remain unrecognized in older adults.[3] Studies report percentages of 4% to 23% for unrecognized HF or COPD in older persons.[4-6] These underlying disorders limit activities of daily living and are associated with a reduced health-related quality of life (HRQoL) and influence prognosis unfavorably.[7] Relief of symptoms, improvement in HRQoL, and maintaining or improving function are key goals in older adults with multimorbidity/polypharmacy.

For COPD and HF, effective interventions exist that may help improve symptoms, functionality, and HRQoL.[8,9] Thus, potentially, a substantial benefit in health outcome could be achieved with identifying these diseases in older men and women. Whether new diagnoses translate into an improved patient health status remains to be established, especially in an older population with multimorbidity and polypharmacy. To address this issue, we performed a cluster randomized clinical trial (RCT) assessing the effectiveness of a case-finding strategy for detecting unrecognized HF or COPD in suspected primary care patients and its effects on treatment decisions and quality of life, physical health status, and health care use after 6 months of follow-up. The strength of such a trial is that all positive and negative consequences (both intended and unintended) associated with case-finding can be observed.

Methods

Trial design

We performed a clustered randomized trial on the effectiveness of a case-finding strategy, with general practices as the unit of randomization. Eighteen group practices of general practitioners (GPs) were randomly allocated to either the case-finding strategy (8 practices) or usual care (10 practices). Randomization was considered necessary because we aimed to quantify the clinical effectiveness of case-finding strategy (ie, test results followed by treatment based on results) on patient outcomes.[10-12] A cluster randomization was chosen to avoid contamination of the GP and participants between the 2 strategies. The study protocol has been published previously.[13]

Study population

General practices from the vicinity of Utrecht, the Netherlands, were eligible for participation. In the Netherlands, all citizens, with the exception of those living in a nursing home or hospice, are registered with a GP, irrespective of treatment by a medical specialist. The general practices were representative for the Netherlands.

Community-dwelling men and women aged 65 years and older were selected from the electronic medical files of the participating GPs. *Multimorbidity* and *polypharmacy* were defined as having 3 or more chronic or vitality-threatening diseases and using 5 or more drugs daily during the previous year, respectively. Patients were excluded if they (1) already had a dual diagnosis of both HF *and* COPD, adequately established according to recent guidelines; (2) had severe cognitive problems; or (3) were unable to visit the GP practice.

Patients willing to participate filled out the Medical Research Council (MRC) dyspnea scale and a short questionnaire about reduced exercise tolerance (Appendix 1).[14] Those who scored positively on the reduced exercise tolerance questionnaire or had 2 or more points on the MRC dyspnea scale (ie, they were troubled by shortness of breath when hurrying on the flat or walking up a slight hill) were eligible for inclusion.

The study was approved on 19 May 2010 by the medical ethics committee of the University Medical Center Utrecht, the Netherlands, and all participants signed informed consent.

Interventions

At the first appointment, depending on the randomization, participants received detailed information regarding the study procedures.

Case-finding strategy. In the intervention group, all participants underwent the case-finding strategy, consisting of the following components: (1) standardized medical history taking and physical examination, (2) blood tests, (3) electrocardiography (ECG), (4) spirometry (Welch Allyn SpiroPerfect), and (5) echocardiography with a mobile device (Vivid-I; General Electric, Milwaukee, WI). Echocardiography was performed by a trained sonographer and interpreted by an experienced cardiologist blinded to other test results.

All tests were performed in a setting close to the home of the participant, this usually being the general practice. After the investigations were completed, the GP received all results, including new diagnoses established by an expert panel (see below), together with an advice on patient management (from the same expert panel) based on recommendations from international clinical guidelines.[8,9] GPs were advised to follow the recommendations, but they were free to adapt to individual circumstances to allow for tailor-made, shared-decision–based management taking into consideration the multimorbidity and polypharmacy of the participants.

Usual care. In the control group, the participating GP only received the answers the participants provided to the questionnaires about possible symptoms (the scores on the MRC dyspnea scale and the exercise tolerance questionnaire). It was then up to the discretion of the GP to decide whether they would proactively perform additional investigations or change the management based on this information.

Outcomes

We first compared the number of newly detected clinically relevant diagnoses in both groups and then evaluated the effects of the case-finding intervention strategy on HRQoL, functionality, and health care use compared to usual care during the 6-month follow-up period.

Newly detected disorders. In the case-finding strategy group, the final diagnoses were established by a panel consisting of 3 clinical experts: a cardiologist (alternating between M. J. M. C., M. A. N. S., and C. G. K. M. F.), a pulmonologist (alternating between J. W. J. L.

and H. J. H.), and an experienced GP (F. H. R.) using the results of all investigations and the information from the electronic medical file of the GP during the follow-up period. Diagnoses were based on consensus after plenary discussion.[15] The diagnosis of HF was established applying the latest criteria from the European Society of Cardiology.[9] Importantly, special attention was paid to diagnose HF with preserved ejection fraction (HFpEF). COPD was diagnosed according to the GOLD criteria.[8]

New diagnoses in the usual care group during the 6-month follow-up period were obtained by scrutinizing the electronic medical file of the GP allocated to this group including searching the free text information for diagnoses.

Health-related quality of life. HRQoL was measured using the Short Form–36 (SF-36)[16] and the EuroQol-5 Dimensions (EQ-5D)[17] questionnaires. The SF-36 is divided into 8 subscales: physical functioning (PF), social functioning (SF), limitations in usual role activities due to physical problems (RP), limitations in usual role activities due to emotional problems (RE), bodily pain (BP), general health (GH), vitality (VT), and mental health (MH), and 2 summary scores: physical component summary (consisting of PF, RP, BP, and GH) and mental component summary (consisting of VT, SF, RE, and MH), ranging from 0 and 100.

The EQ-5D is a questionnaire with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These dimensions are divided into 3 degrees of severity: "no problem," "some problems," or "major problems." A single index score can be produced using information from these 5 dimensions.

For both questionnaires, higher scores indicate a better HRQoL. All participants filled out both questionnaires at baseline and after 6 months of follow-up.

Functional health status. Self-reported activities of daily living (ADL) were measured with the Katz-15[18] at baseline and after 6 months of follow-up. The ADL scale assesses 15 functions: bathing, dressing, grooming, toileting, mobility (rising from a chair and walking), continence, feeding, use of a telephone, transportation, shopping for groceries, preparation of a meal, household activities, taking medications as prescribed, and managing money. The Katz-15 outcome was a 0-15 scale of number of dependencies, with a score of 15 representing dependencies in all activities. Participants were categorized into either "fully independent" or "any grade of dependence" for ADL. *Fully independent* was defined as a score of zero.

Health care use. All participants filled out the Minimal Data Set of the Dutch National Care for the Elderly Program (ZonMw-NPO)[19] at baseline and after 6 months of follow-up, which included questions about their use of home care, admission to home for the elderly or nursing home, and GP visits during out-of-office hours.

After 6 months, the GPs' electronic medical files of all participants were checked for changes in medication and health care use (ie, GP visits, outpatient visits, and hospitalizations) during the follow-up period of 6 months.

Patient involvement

The outcome measures of this research were submitted to the elderly panel and delegation of the Network Utrecht Elderly Care attached to the Dutch National Care for the Elderly Program. Their preference for the outcome measure was quality of life. Patients were not involved in the design, recruitment, and conduct of the study. The results will be disseminated through the GPs, researchers, and newsletters of the Network Utrecht Elderly Care. The burden of the intervention (ECG, echocardiography, and spirometry) was assessed with the visual analog scale by every patient in the case-finding strategy.

Sample size

We estimated that, with our case-finding intervention strategy, at least 15% of the population under study would be diagnosed with either HF or COPD.[20] To detect a 10% difference between the 2 groups in diagnoses of HF and/or COPD, using an α of .05, a power of 0.80, and an intracluster correlation coefficient of 0.05,[21] 301 participants per group were needed. Considering a dropout of at least 10%, we aimed to include 400 participants in each group (total of 800). We calculated that around 35 general practices with each around 2400 citizens enlisted (16% older than 65 years, of whom 6% are expected to meet our definition of multimorbidity/polypharmacy) would be needed to recruit a total of 800 multimorbid older persons with dyspnea or reduced exercise tolerance.[22]

Randomization

General practices were the units of randomization in our cluster randomized trial. The allocation schedule for random assignment of either the case-finding strategy or usual care to the general practices was computer generated, using the minimization method applied by an employee of the Data Management department of the UMC Utrecht Julius Center. Size of the practice (number of enlisted men and women) was the only factor used in the minimization to ensure that the 2 groups were balanced in the number of participants.

The first practice was randomized in June 2010, after approval of the medical ethics committee and registration in the trial register.

Blinding

We applied no active measures for blinding the group assignment. The GPs were invited to participate in a study aimed at detecting unrecognized HF and COPD. If they agreed to participate, their practice was randomized, and they only received detailed information about the group their practice was randomized to. This strategy of selective information was chosen to avoid contamination (ie, that GPs in the usual care group could be triggered to deviate from usual care and perform similar diagnostic tests as in the GPs allocated to the case-finding strategy).

Data analysis

Demographic and clinical characteristics of patients across the 2 intervention groups are presented as means or proportions. Subsequent treatment decisions during 6 months are presented as proportions. Comparison of the continuous outcomes (EQ-5D, SF-36 scales, KATZ-15) between the 2 strategies was done using a linear mixed model. The analysis included baseline measurements of the continuous outcomes as a covariate and a random intercept to correct for clustering of patients in practices and expressed as adjusted differences in means with 95% CIs.[23] Comparison of the dichotomous outcomes, that is, newly detected diagnoses (primary outcome) and health care use, was analyzed applying a log binomial mixed model and expressed as adjusted relative risk with 95% CIs.[23,24] Count outcomes (such as the number of hospital visits) were analyzed with generalized linear models for negative binomial distributions and expressed as adjusted rate ratios with 95% CIs. For the dichotomous and count outcomes, a residual (ie, Generalized Estimating Equations (GEE)) covariance matrix was incorporated in the model to account for clustering.[25,26]

The number of missing values at baseline was low (≤1%). At follow-up, in 45 (5.4%) patients, all questionnaires were missing (see Appendix 2 for differences in baseline characteristics), and in 6 (0.8%) patients, some questionnaires were missing. In patients who filled out all the questionnaires at follow-up (n = 778), missings were low (≤1.5%). For patients who died (n = 10), HRQoL scores at follow-up were imputed as zero. To prevent biased results due to incomplete data and selective loss to follow-up, we performed multiple imputation of missing HRQoL and functional health values prior to the regression analysis using regression methods.[27-29] From 5 imputation sets, the pooled estimates were calculated. All data, except for the difference in means and risk ratios, are presented as crude estimates.

Data were analyzed using SPSS software (version 20.0 for Windows; SPSS Inc, Chicago, IL) and SAS software (version 9.2; SAS, Cary, NC).

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Table I. Sociodemographic and clinical characteristics of 829 frail elderly with dyspnea or reduced exercise tolerance in the screening strategy and usual care group

	Screening strategy (n = 389)	Usual care (n = 440)
Mean age, y ± SD	75.5 ± 6.1	74.1 ± 6.3
Male sex, n (%)	174 (44.7)	238 (54.1)
Living situation, n (%)†		
Independent, alone	128 (33.0)	146 (33.3)
Independent, with others	256 (66.0)	289 (65.8)
Home for the elderly	4 (1.0)	4 (0.9)
Marital status, n (%)†		
Never married	9 (2.3)	11 (2.5)
Previously married	120 (30.9)	139 (31.7)
Presently married or in marriage-like relationship	259 (66.8)	289 (65.8)
Level of education, n (%)‡		
Primary education	51 (13.1)	52 (11.9)
Secondary education	271 (69.8)	291 (66.7)
Tertiary education	66 (17.0)	93 (21.3)
Medical history, n (%)		
Ischemic heart disease	125 (32.1)	131 (29.8)
Hypertension	287 (73.8)	294 (66.8)
Diabetes Mellitus	129 (33.2)	130 (29.5)
Stroke or TIA	44 (11.3)	55 (12.5)
Visual impairment	95 (24.4)	109 (24.8)
Hearing impairment	40 (10.3)	49 (11.1)
Medication at baseline, n (%)		
Spironolactone	23 (5.8)	21 (4.8)
Loop diuretics	53 (13.6)	68 (15.4)
Thiazide diuretics	156 (40)	158 (35.9)
ACE-I or ARBs	218 (56.0)	253 (57.5)
β-Blockers	183 (47.0)	208 (47.3)
Inhaled long-acting β2-agonists	59 (15.2)	81 (18.4)
Inhaled anticholinergic	49 (12.6)	52 (11.8)
Inhaled corticosteroids	57 (14.7)	84 (19.1)
HRQoL score at baseline, mean (SD)‡		
PCS	40.5 (9.8)	39.6 (10.2)
MCS	52.1 (9.2)	52.2 (9.9)
EQ-5D	0.80 (0.17)	0.79 (0.16)
Functional health at baseline, n (%)*		
Katz-15 any dependency	194 (49.9)	208 (47.3)

Previously married included divorced or widower; level of education was divided into primary, 6 or less classes of primary school; secondary, more than primary, practical training or secondary school; and tertiary, (pre-)university school. Ischemic heart disease included prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention. Visual impairment included cataract, blindness, or glaucoma. Diuretics included loop, thiazide, and potassium-sparing diuretics. *ACE-I*, angiotensin-converting enzyme inhibitor; *ARBs*, angiotensin receptor blockers; *PCS*, physical component summary; *MCS*, mental component summary.

Results

Across all general practices, a total of 1,249 elderly persons were willing to participate, of whom 841 (67%) had complaints of dyspnea or reduced exercise tolerance (see Appendix Figure 1 for the flow diagram of the study). More patients were eligible and willing to participate than initially expected.

Older persons with multimorbidity/polypharmacy with complaints included in the study were slightly younger, but they were comparable in terms of gender (Appendix 3). Patient recruitment started in June 2010 and ended in January 2012. Of the 841 persons eligible, 12 patients (6 per group) withdrew after having already given informed consent. In Table I, the baseline characteristics of the remaining 829 randomized participants are presented, stratified per group (389 in the case-finding strategy group and 440 in the usual care group). The patients in the case-finding strategy were on average 1 year older (75.5 vs

Table II. Number and type of new diagnoses detected during 6 months of follow-up

	Screening strategy* (n = 389)	Usual care* (n = 440)
Any new diagnoses, n (%)	226 (58.1)	74 (16.8)
Heart failure	127 (33.5)	9 (2.0)
COPD	65 (16.8)	10 (2.3)
Atrial fibrillation	7 (1.8)	15 (3.4)
Valvular disease	81 (21.4)	18 (4.1)
Asthma	12 (3.1)	5 (1.1)
Anemia	49 (12.7)	16 (3.6)
Hypothyroidism	1 (0.3)	4 (0.9)
Hyperthyroidism	1 (0.3)	3 (0.7)

In the screening strategy, 343 new diagnoses were detected in 226 patients: 142 patients had 1, 61 patients had 2, 14 had 3, 8 had 4, and 1 patient had 5 new diagnoses. In usual care, 80 new diagnoses were detected in 74 patients: 68 patients had 1 and 6 patients had 2 new diagnoses. Because of an incomplete screening strategy or a nonassessable test, we had 10 missings on heart failure, 3 on COPD, 11 on valvular disease, 4 on asthma, 3 on anemia, and 6 on hypo- and hyperthyroidism.

74.1 years) and less often male (45% vs 54%). Six patients (1.5%) in the case-finding strategy and 4 (0.9%) patients in the usual care group died.

Newly detected disorders

In the case-finding strategy, 343 new diseases were detected in 226 (58.1%) participants. The main diagnoses were HF (cumulative 6-month incidence 33.5% (95% CI 28.8%-38.2%), of whom 28% (36 participants) had HF with reduced ejection fraction and 70% (89 participants) had HFpEF, COPD (16.8% [95% CI 13.1%-20.5%]), and clinically relevant valvular heart disease (21.4% [95% CI 17.3%-25.5%]). In the usual care group, there were 74 (16.8%) participants with 1 or more newly diagnosed diseases (Table II). The cumulative 6-month incidence was 2.0% (95% CI 0.7%-3.3%) for HF and 2.3% (0.9%-3.7%) for COPD.

Subsequent treatment decisions

In Appendix 4, the changes in treatment within 6 months of follow-up in patients with a new diagnosis of HF or COPD with the case-finding strategy are presented. For participants in the case-finding strategy, the panel advised to start or adjust pharmacotherapy in 74 (58.3%) patients with a new diagnosis of HF. Advice was adopted by the GP in 33 (44.6%) of these patients. For patients with a new diagnosis of COPD, the panel advised to initiate novel inhaled medication in 35 (53.8%) patients, and this advice was adopted by the GP in 16 (45.7%). In Appendix 5, the treatment changes per study arm are presented in more detail.

HRQoL and functional health status

In Table III, the baseline and follow-up scores on the SF-36, EQ-5D, and KATZ-15 are presented. The scores were in general somewhat higher for the usual group although not clinically relevant or statistically significant. In general, the scores of HRQoL declined during follow-up, but the crude score of the EQ-5D after 6 months was higher than at baseline. In both groups, approximately 7% of the patients improved from any dependency to fully independent on ADL at follow-up.

An improvement of the MRC dyspnea scale was observed in 41.7% of the patients in the case-finding strategy and 37.5% of the patient in the usual care group (risk ratio [RR] 1.1 [95% CI 0.9-1.3]).

Health care use

During 6 months of follow-up, there were overall no differences in health care use between the 2 groups, as shown in Table IV. Of those allocated to the case-finding strategy, more patients visited the GP at least once during office hours (96.7% vs 91.4%; RR 1.06 [95% CI 1.02-1.11]). The number of patients visiting hospital outpatient clinics was nonsignificantly lower in the case-finding strategy compared to the usual care group (47.6% vs 55.2%; RR 0.87 [95% CI 0.74-1.03]).

Patient involvement

The burden of intervention was deemed to be low by patients with a median visual analog scale score for electrocardiogram of 6 (IQR 2-10) and 2 (IQR 2-4) for echocardiography on a scale from 0 to 100.

Discussion

Summary

To our knowledge, this is the first large-scale diagnostic RCT comparing a case-finding strategy with usual care regarding patient-reported relevant health outcomes in older adult persons with multimorbidity/polypharmacy presenting with dyspnea or reduced exercise tolerance. Case-finding identified many new diseases (especially HFpEF [23.5%], valvular heart disease [21.4%], and COPD [16.8%]), but the large difference in case-finding–detected diagnoses did not result in clinically relevant differences in the patients' quality of life, functional status, or health care consumption during the 6-month follow-up period.

Comparison with existing literature

Our randomized trial confirms the underdiagnosis of HF and COPD in community-dwelling older persons.[30,31] In more than half (58%) of the participants in the case-finding strategy, a previously unrecognized disease was detected.

There are several plausible reasons for the "mismatch" between the number of novel diagnoses detected and the lack of a beneficial effect of these findings on patient outcomes. First, because of our population of interest, most participants were known to have diseases (ie, hypertension, atrial fibrillation, diabetes) for which cardiovascular drugs were already prescribed. The same

Table III. Observed baseline and follow-up scores on HRQoL and functional health in 829 frail elderly with dyspnea or reduced exercise tolerance, divided by screening strategy and usual care

	Baseline†		Follow-up†		Difference* (95% CI)
	screening strategy (n = 389)	Usual care (n = 440)	screening strategy (n = 389)	Usual care (n = 440)	
HRQoL					
EQ-5D, mean (SD)	0.80 (0.17)	0.79 (0.16)	0.90 (0.14)	0.91 (0.11)	–0.01 (–0.04 to 0.02)
SF-36 scale					
PCS, mean (SD)	40.5 (9.8)	39.6 (10.2)	40.5 (9.8)	40.3 (10.0)	–0.7 (–1.6 to 0.3)
MCS, mean (SD)	52.1 (9.2)	52.2 (9.9)	51.3 (9.6)	52.2 (9.0)	–0.9 (–2.3 to 0.4)
PF, mean (SD)	59.6 (22.9)	59.4 (24.4)	58.8 (24.1)	60.9 (24.2)	–2.8 (–6.0 to 0.3)
RP, mean (SD)	55.5 (41.8)	53.7 (41.1)	57.4 (40.9)	57.5 (39.6)	–1.2 (–5.9 to 3.5)
BP, mean (SD)	72.5 (24.2)	69.9 (23.2)	71.5 (23.7)	70.8 (23.5)	–1.2 (–4.2 to 1.8)
GH, mean (SD)	53.4 (16.1)	52.5 (16.1)	53.4 (16.9)	53.8 (16.9)	–1.5 (–3.5 to 0.5)
VT, mean (SD)	61.3 (16.1)	59.5 (17.5)	58.9 (16.9)	59.9 (17.1)	–2.3 (–5.3 to 0.7)
SF, mean (SD)	76.9 (21.8)	75.6 (23.0)	76.5 (23.5)	75.9 (20.9)	–1.0 (–4.9 to 3.0)
RE, mean (SD)	75.5 (37.7)	76.7 (37.3)	72.4 (38.7)	78.3 (34.8)	–6.0 (–11.0 to –0.9)
MH, mean (SD)	74.4 (15.7)	74.8 (15.9)	74.0 (15.3)	75.1 (15.6)	–1.0 (–3.0 to 1.0)
Functional health					
Katz-15, mean (SD)	1.2 (1.8)	1.0 (1.4)	1.3 (1.9)	1.1 (1.5)	0.1 (–0.1 to 0.3)

* Difference in follow-up scores are estimates from the linear mixed models taking into account clustering and baseline score. At baseline, we had 1 missing for KATZ-15; 2 for PF, GH, SF, and MH; 3 for RP, BP, and VT; 4 for RE; and 5 for EQ-5D, PCS, and MCS. At follow-up, we had 45 missings on PF, GH, SF, MH, BP, and VT; 47 on EQ-5D; 48 on RE; 49 on RP; 50 on KATZ-15; and 53 on PCS and MCS.

Table IV. Health care use of 829 frail elderly with dyspnea or reduced exercise tolerance, divided by screening strategy and usual care during 6 months of follow-up

	Screening strategy (n = 389)	Usual care (n = 440)	RR† (95% CI)
GP visits,‡ n (%)	376 (96.7)	402 (91.4)	1.06 (1.02-1.11)
Mean number	5.2	4.5	1.16 (0.96-1.40)
GP investigations, n (%)	212 (54.5)	261 (59.3)	0.95 (0.74-1.23)
Number, means (SD)	0.8 (1.0)	1.0 (1.1)	0.91 (0.60-1.39)
Blood test, n (%)	193 (49.6)	241 (54.8)	
ECG, n (%)	22 (5.7)	21 (4.8)	
Spirometry, n (%)	24 (6.2)	33 (7.5)	
Echocardiography, n (%)	9 (2.3)	4 (0.9)	
GP visits during out-of-office hours,* n (%)	113 (31.1)	132 (32.3)	0.99 (0.75-1.31)
Hospital outpatient visits, n (%)	185 (47.6)	243 (55.2)	0.87 (0.74-1.03)
Mean number	0.8	1.0	0.79 (0.64-0.98)
Cardiology, n (%)	60 (15.4)	86 (19.5)	
Pulmonary, n (%)	26 (6.7)	24 (5.5)	
Other, n (%)	130 (33.4)	196 (44.5)	
Hospital admissions, n (%)	50 (12.9)	52 (11.8)	1.10 (0.74-1.63)
Mean no. of days	1.1	0.8	1.40 (0.82-2.40)
Cardiology, n (%)	7 (1.8)	13 (3.0)	
Pulmonary, n (%)	4 (1.0)	2 (0.5)	
Other, n (%)	39 (8.0)	37 (8.4)	
Use of home care,* n (%)	73 (20.1)	71 (17.4)	1.15 (0.96-1.38)
Admissions to home for the elderly or nursing home,* n (%)	4 (1.1)	4 (1.0)	1.24 (0.96-3.41)

The numbers and percentages mentioned under GP investigations were performed apart from the screening strategy. *RR*, relative risk for dichotomous outcomes and rate ratio for count outcomes. We had 57 missings on GP visits during out-of-office hours, 2 missings on hospital days, and 59 missings on use of home care and on admission to home for the elderly or nursing home.

drugs are also used in the management of HF with reduced ejection fraction, HFpEF, and valvular heart disease, which leave little room for the initiation of drugs in patients with a case-finding–detected diagnosis of heart failure or clinically relevant valvular disease.[32] Consequently, the expert panel's advice usually concerned adjustment of medication regimens. Secondly, both the GP and the patient may be reluctant to change management based on a "nonsuspected case-finding–detected diagnosis" in older adults with multiple comorbidities or polypharmacy because of fear of a cascade of negative effects due to drug interactions or adverse

effects such as drop in blood pressure or further renal deterioration. This may result in an explicit decision, reached during shared-decision making, to refrain from changes in patient management.[33] Third, our study population differs considerably from participants in large RCTs on drug treatment in HF and COPD. For example, participants in RCTs evaluating drugs for COPD or HF had a mean age of 62 years, whereas this was 75 years in our participants' population.[8,9] Moreover, participants in drug RCTs often have no or limited comorbidity. Community-dwelling elderly with multimorbidity and polypharmacy are hardly ever included in large drug RCTs.[34] A fourth reason for the lack of change in patient outcomes after 6 months in our study is the fact that the majority of newly detected cases of HF had preserved cardiac ejection fractions (70% of all new cases of HF) and effective evidence-based mortality- and morbidity-reducing drug treatment is lacking for these patients. Thus, their treatment is empirically based on reduction of symptoms of fluid overload, controlling blood pressure, and managing heart rate in those with tachycardia.[9] Fifth, potential beneficial effects may not have been achieved as the treatment advice provided by the expert panel was not followed by the GP in less than half (45%) of the cases. This may have been because these patients identified perhaps had a milder form of disease, either HF or COPD. Subsequently, this may mean that these diseases may have less of an impact on patient outcomes, particularly in the short term, than more severe forms of disease which have impacted patients significantly enough to result in them seeking health care. A sixth reason is that as the sample size calculations were based on having sufficient power to look into differences in prevalence of HF/COPD between the 2 groups, there may not be sufficient power to be able to accurately exclude a difference in outcome at 6 months. Additionally, a follow-up period of 6 months may have been too short to exert an effect upon HRQoL, functional health status, and use of health care resources.

Finally, the study itself may have created bias in the way the GPs provide their "usual care" once they found out about the aims and objectives of the trial because they may be inherently more active in searching for such diagnoses, thus diluting the effect of the actual intervention. However, the GP did not know exactly what the intervention in the intervention arm would be, and it was up to their discretion to decide whether they would proactively perform additional investigations or change the management based on this information. In both arms, similar frequencies of investigations were performed over the 6 months, likely driven by patients' symptoms and signs implying that the usual care group was actually rather similar to "real" usual care.

Of those allocated to the case-finding strategy, more patients visited the GP at least once during office hours than in the usual care strategy. This may be explained by the fact that the case-finding pathway involved a number of investigations that had to be performed such as echocardiography, all of which are usually performed during office hours. The number of patients visiting hospital outpatient clinics was lower in the case-finding strategy compared to the usual care group. This may be because, as mentioned above, investigations such as spirometry and echocardiography were part of the pathway of the case-finding strategy, so these patients were less likely to be referred to secondary care for the purpose of said investigations. However, the investigations performed by the GP in the usual care group were up to the GPs' discretions; therefore, they may have more likely to have referred patients to secondary care for these investigations.

Strengths and limitations

The major strength of our study is that this is the first randomized trial directly comparing a case-finding strategy with usual care while focusing on "real-life" management changes and effects on relevant patient outcomes. This is in contrast to nearly all previously published diagnostic and screening studies that stopped at the point of diagnosis.[3,35] From that point onward, potential (beneficial) effects on patient outcomes are then often "extrapolated" by applying results from previous drug RCTs (linked-evidence approach).[36] By directly comparing our case-finding strategy in a randomized manner to usual care, we were able to quantify subsequent changes in patient management and outcomes attributable to the case-finding strategy.[37]

A potential limitation of our study is that we deliberately allowed the GP to adapt the advice provided by the expert panel and recommended in the prevailing clinical guidelines in their patient management. Although this may have reduced the effects on patient outcomes, we believe such a pragmatic approach was important because a patient-tailored shared-decision approach is needed in this high-risk population. For our trial, we selected 4,142 persons with multimorbidity/polypharmacy, of whom 30% were willing to participate, a number that is comparable to other screening or case-finding studies performed in community-dwelling persons and that even could be considered high when realizing the frailty of the participants. Importantly, the number of missing variables during 6 months of follow up was very low. Another limitation is that we restricted the number of investigations that could be performed within our case-finding strategy. We therefore could not detect other diseases that may account for dyspnea and reduced exercise tolerance, such as angina pectoris, obstructive sleep apnea, and "deconditioning." A new diagnosis was based on information available in the electronic medical files in the usual care arm. This was also the case in the intervention arm but in addition to diagnoses established by the expert panel. There could therefore be relatively

more underregistration of diagnoses in the usual care arm. Our sample size calculation was based on the newly detected diseases in the case-finding strategy and not on HRQoL and functional health. The effects on these outcomes were difficult to estimate for our study population. The effect that we found on HRQoL and functional health was small and had no clinical relevance. If we had a longer follow-up period, we hypothesize that this would not have changed our conclusion. As mentioned, a longer follow-up may result in a greater difference in patient outcomes; however, the use of patient-reported outcomes and not hard end points is an advantage because this most accurately represents improvement in health from a patient's perspective. Originally, we had planned a cost-effectiveness analysis as mentioned in our design paper,[13] but because of a lack of effect on health-related QoL, functionality, GP visits, hospital outpatient visits, or hospitalizations (Tables III and IV) between the arms during 6-month follow up, we decided not to because the screening intervention could not be cost-effective due to the lack effects on clinically relevant outcomes.

Implications for research and practice

Case-finding for HF and COPD in older multimorbid persons with dyspnea or reduced exercise tolerance led to a substantial number of new diagnoses but did not result in a change in patient management in the majority of the cases or in improved functional health or quality of life after 6 months of follow-up compared to usual care.

We conclude that a diagnostic workup for patients with symptoms detected with a questionnaire does not affect management in the short term.

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Authors' contributions

Y. v. M. was responsible for the data acquisition, analysis, and interpretation and drafted the article. F. H. R. raised funding; was panel member; and participated in the conception, design, data acquisition and interpretation, and revision of the article. J. B. R. and A. G. interpreted the data and revised the article. L. C. M. B. participated in data acquisition, interpretation, and revision of the article. M. J. M. C. and J. W. J. L. were panel members and revised the article. K. G. M. M. and A. W. H. helped to raise funding and are responsible for conception and design of the study and revision of the article. All authors read and approved the final draft of the manuscript.

Disclosures

All authors declare no competing interests.

References

1. Mulrow CD, Lucey CR, Farnett LE. Discriminating causes of dyspnea through clinical examination. J Gen Intern Med 1993;8(7):383-92.
2. van Mourik Y, Rutten FH, Moons KG, et al. Prevalence and underlying causes of dyspnoea in older people: a systematic review. Age Ageing 2014 May;43(3):319-26.
3. Nielsen LS, Svanegaard J, Wiggers P, et al. The yield of a diagnostic hospital dyspnoea clinic for the primary health care section. J Intern Med 2001;250(5):422-8.
4. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;25 (18):1614-9.
5. Hancock HC, Close H, Mason JM, et al. High prevalence of undetected heart failure in long-term care residents: findings from the Heart Failure in Care Homes (HFinCH) study. Eur J Heart Fail 2013;15 (2):158-65.
6. Van Durme YM, Verhamme KM, Stijnen T, et al. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. Chest 2009;135(2):368-77.
7. Ho SF, O'Mahony MS, Steward JA, et al. Dyspnoea and quality of life in older people at home. Age Ageing 2001;30(2):155-9.
8. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. Available from: http://www.goldcopd.org/. 2011.
9. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33(14):1787-847.
10. Moons KG, Altman DG, Vergouwe Y, et al. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606.
11. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart 2012;98(9):691-8.
12. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. Ann Intern Med 2006;144(3):201-9.
13. van Mourik Y, Moons KG, Bertens LC, et al. Triage of frail elderly with reduced exercise tolerance in primary care (TREE). a clustered randomized diagnostic study. BMC Public Health 2012;12:385.
14. Fletcher CM, Elmes PC, Fairbairn AS, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959;2(5147):257-66.
15. Bertens LC, Broekhuizen BD, Naaktgeboren CA, et al. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. PLoS Med 2013;10(10), e1001531.

16. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.
17. Brooks RG, Jendteg S, Lindgren B, et al. EuroQol: health-related quality of life measurement. Results of the Swedish questionnaire exercise. Health Policy 1991;18(1):37-48.
18. Weinberger M, Samsa GP, Schmader K, et al. Comparing proxy and patients' perceptions of patients' functional status: results from an outpatient geriatric clinic. J Am Geriatr Soc 1992;40(6):585-8.
19. Lutomski JE, Baars MA, Schalk BW, et al. The Development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): a large-scale data sharing initiative. PLoS One 2013;8(12), e81673.
20. Rutten FH, Moons KG, Cramer MJ, et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ 2005;331(7529): 1379.
21. Campbell MJ. Cluster randomized trials in general (family) practice research. Stat Methods Med Res 2000;9(2):81-94.
22. Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. *Bilthoven: RIVM,* www.nationaalkompas.nl. 2012.
23. Groenwold RH, Moons KG, Peelen LM, et al. Reporting of treatment effects from randomized trials: a plea for multivariable risk ratios. Contemp Clin Trials 2011;32(3):399-402.
24. Knol MJ, Le CS, Algra A, et al. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012;184(8):895-9.
25. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrics 1986;73(1):13-22.
26. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42(1):121-30.
27. Donders AR, van der Heijden GJ, Stijnen T, et al. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59(10):1087-91.
28. Groenwold RH, Donders AR, Roes KC, et al. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol 2012;175(3):210-7.
29. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367(14):1355-60.
30. Bednarek M, Maciejewski J, Wozniak M, et al. Prevalence, severity and underdiagnosis of COPD in the primary care setting. Thorax 2008;63(5):402-7.
31. Wheeldon NM, MacDonald TM, Flucker CJ, et al. Echocardiography in chronic heart failure in the community. Q J Med 1993;86(1): 17-23.
32. Gijsen R, Hoeymans N, Schellevis FG, et al. Causes and consequences of comorbidity. a review J Clin Epidemiol 2001;54(7):661-74.
33. Mamede S, Schmidt HG. The twin traps of overtreatment and therapeutic nihilism in clinical practice. Med Educ 2014;48(1):34-43.
34. Oudejans I. *Heart failure in geriatric outpatient.* Thesis. 2012.
35. Pedersen F, Mehlsen J, Raymond I, et al. Evaluation of dyspnoea in a sample of elderly subjects recruited from general practice. Int J Clin Pract 2007;61(9):1481-91.
36. Koffijberg H, van ZB, Moons KG. From accuracy to patient outcome and cost-effectiveness evaluations of diagnostic tests and biomarkers: an exemplary modelling study. BMC Med Res Methodol 2013;13:12.
37. Bossuyt PM, Irwig L, Craig J, et al. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ 2006;332 (7549):1089-92.