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Comprehensive care programs for patients with multiple chronic conditions: A systematic literature review

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ABSTRACT

Objective: To provide insight into the characteristics of comprehensive care programs for patients with multiple chronic conditions and their impact on patients, informal caregivers, and professional caregivers.

Methods: Systematic literature search in multiple electronic databases for English language papers published between January 1995 and January 2011, supplemented by reference tracking and a manual search on the internet. Wagner's chronic care model (CCM) was used to define comprehensive care. After inclusion, the methodological quality of each study was assessed. A best-evidence synthesis was applied to draw conclusions.

Results: Forty-two publications were selected describing thirty-three studies evaluating twenty-eight comprehensive care programs for multimorbid patients. Programs varied in the target patient groups, implementation settings, number of included interventions, and number of CCM components to which these interventions related. Moderate evidence was found for a beneficial effect of comprehensive care on inpatient healthcare utilization and healthcare costs, health behavior of patients, perceived quality of care, and satisfaction of patients and caregivers. Insufficient evidence was found for a beneficial effect of comprehensive care on health-related quality of life in terms of mental functioning, medication use, and outpatient healthcare utilization and healthcare

costs. No evidence was found for a beneficial effect of comprehensive care on cognitive functioning, depressive symptoms, functional status, mortality, quality of life in terms of physical functioning, and caregiver burden.

Conclusion: Because of the heterogeneity of comprehensive care programs, it is as yet too early to draw firm conclusions regarding their effectiveness. More rigorous evaluation studies are necessary to determine what constitutes best care for the increasing number of people with multiple chronic conditions.

1. INTRODUCTION

Chronic diseases are the leading cause of disability and death in the western part of the world [1]. Over the coming years, the prevalence of chronic diseases is predicted to increase because of the rapid ageing of the world population and the greater longevity of people with chronic conditions [2–4]. An increasing proportion of the chronically ill is multimorbid [5,6]. The term “multimorbidity” refers to any co-occurrence of multiple chronic conditions within one person, and is to be distinguished from the term “co-morbidity” which refers to the combination of additional diseases beyond an index disorder [6–8]. The prevalence of multiple chronic conditions among individuals increases with age and is substantial among older adults [5]. In people over age 65 about 65% is multimorbid; in people over age 85 this proportion is about 85% [6,8,9].

Having multiple chronic conditions is associated with poor quality of life, disability, psychological distress, and an increased mortality risk [6,10]. The complex healthcare needs of most patients with multiple chronic conditions usually require the involvement of a large number of healthcare providers in the care process.

Coordination of care is therefore difficult and healthcare providers often fail to address the integral healthcare demand, including psychosocial issues, of patients with multiple chronic conditions [8,11–13]. As a result, multimorbid patients are prone to receive fragmented, incomplete, inefficient, and ineffective care, which in turn may lead to unnecessary hospitalizations, increased use of emergency facilities, polypharmacy, adverse drug events, duplicative tests, and conflicting medical advices [5,8,14,15].

Increasingly, comprehensive care programs are implemented in healthcare systems worldwide to address the integral healthcare demand of multimorbid patients [5,16,17]. Models are considered to be comprehensive if they address several healthcare needs of people with multiple chronic conditions, functional disabilities, and/or high healthcare utilization and if healthcare services are provided by multiple healthcare providers [17]. Comprehensive care programs are patient-centered and aim to structure and coordinate delivery of healthcare services [5,16,17]. Such programs are referred to as e.g. integrated care programs, disease management programs, guided care, transitional care or shared care [13,17]. By improving quality and continuity of care, these programs aim to improve patient health outcomes, whilst making efficient use of healthcare resources [13,18,19].

Reviews that provide an overview of implemented comprehensive care programs for patients with multiple chronic conditions indicate that evidence for their impact on patients and caregivers is inconsistent [17,20–25]. In most of these reviews criteria for the inclusion of studies were rather narrow. Some reviews predominantly

included randomized controlled trials [17,21,23], whereas others just evaluated the impact of programs on patient outcomes [17,23–25] or included studies suggesting positive effects of comprehensive care programs [17]. Furthermore, most reviews provide limited information about the contents of the comprehensive care programs included. As a result, relevant information from non-randomized trials and information about the impact of programs on caregiver outcomes have hardly been summarized yet. Moreover, little is known about the program characteristics that may be related to positive outcomes of care and about the patient groups that may benefit most from comprehensive care. This information is, however, of importance since interest in what constitutes best care for patients with multimorbidity is growing. We therefore performed a thorough review of the literature using less narrow inclusion criteria than earlier review studies. We aimed to provide more insight into the characteristics of comprehensive care programs for patients with multiple chronic conditions and their impact on patients, informal caregivers, and professional caregivers.

2. METHODS

2.1. Study design and search strategy

We conducted a systematic literature search in the electronic databases Cinahl, Cochrane, Embase, Medline, PsycInfo, and SciSearch. The databases were searched for English language papers focusing on comprehensive care programs for people aged 18 years and older and published between January 1995 and January 2011. January 1995 was used as a starting point since from that year on comprehensive care has become an increasingly important focus of attention in the medical literature [26].

A comprehensive search strategy was developed by a librarian and two members of the project team (SdB and LL) to identify studies matching the following search terms (Medical Subject Headings): case management, comprehensive healthcare, critical pathways, disease management, continuity of patient care, patient care management, planning or team, patient-centered care, delivery of integrated healthcare, guided care, integrated care, managed care (programs), shared care, transmural care and variations of the keywords chronic disease, chronic illness, co-morbidity, frailty, multimorbidity, multiple chronic conditions, and specific chronic conditions. These search terms were combined with variations of the following search terms: benefits, effects, effectiveness, efficacy, impact, outcomes, and specific (health) outcomes. In addition to the search in the electronic databases, relevant papers were identified through reference tracking and through a manual literature search on the internet. The internet was searched if the electronic database search yielded papers that reported on the design of an intervention study or a pilot intervention study. We then searched the internet to determine the status of these studies and to find out whether their results had already been published in scientific papers.

2.2. Study selection

Four reviewers (SdB, NV, LL, CM) worked in pairs and independently reviewed the papers yielded by the search for their relevance by screening their title and abstract.

When considered relevant by both reviewers, the fulltext paper was retrieved. Any disagreement between the reviewers was resolved by consensus. In line with earlier studies [e.g. 27–31], the chronic care model (CCM) of Wagner et al. [18,32] was used to define comprehensive care. The model suggests that comprehensive care programs ideally comprise six interrelated components. Four components refer to the actual delivery of care by healthcare providers:

1. self-management support that helps patients and their families to obtain skills and confidence to manage their chronic condition (e.g. regular health education and coaching);
2. delivery system design that ensures the delivery of effective, efficient patient care through e.g. involvement of all members of the multidisciplinary team, planned patient interactions, regular follow-up, and case management;
3. decision support by evidence-based guidelines providing clinical standards for high-quality chronic care, and
4. development of clinical information systems that supply care teams with feedback, remind them to comply with practice guidelines, provide registries for planning individual and population-based care, and enable proactive interactions between caregivers and patients.

The two remaining components refer to the context in which chronic care is provided: 5. the healthcare system that provides the organizational context in which chronic care is provided and encompasses the aforementioned components. A healthcare system that endorses improvement of the quality of care must be well-organized, motivated, and prepared to change; and 6. links towards community resources and policies. The healthcare system is embedded in a community that includes organizations and programs that may support or expand a healthcare system's care for chronically ill patients (e.g. senior centers that address social issues of patients or fitness centers that offer physical activity programs) [32,33]. In our study, only comprehensive care programs that included interventions related to two or more components of the CCM were included. We decided on a minimum of two components since, according to the CCM, components must be interrelated.

For the present study, papers were eligible if they met the following inclusion criteria: 1. the program described in the paper met our operational definition of comprehensive care; 2. the target population of the program consisted of people with multiple chronic conditions; and 3. the study described in the paper was an intervention study evaluating the impact of a comprehensive care program. Duplicate studies were identified and excluded.

2.3. Data extraction, quality assessment, and data analysis

Four authors (SdB, NV, LL, CM) worked in pairs to extract relevant data from the studies included. Data extracted from the papers were: 1. study design; 2. length of follow-up of study; 3. target population of the program; 4. setting in which the program had been implemented; 5. content of the program described in terms of the CCM components; 6. characteristics of the usual care condition; and 7. study outcomes. Our analyses were descriptive and qualitative in nature.

Of the studies that compared healthcare costs of comprehensive care with those of usual care, we reported the incremental healthcare costs of comprehensive care. Incremental costs can be defined as the difference in healthcare costs for patients receiving comprehensive care and those for patients receiving care as usual. Negative incremental costs imply that healthcare costs for patients receiving comprehensive care are lower than those for patients receiving usual care. Positive incremental costs

imply that healthcare costs for patients receiving comprehensive care are higher than those for patients receiving usual care. For the present paper, we only report incremental direct healthcare costs, such as costs of primary care visits, emergency room (ER) visits, and hospitalization. Cost estimates were adjusted for cross-country purchasing power differences (PPP), using 2008 US\$ PPP, and for inflation, using Gross Domestic Product prices in order to make meaningful comparisons across studies [34]. Four studies did not report the year of data collection. For these studies the year of publication was used as reference year.

The methodological quality of the selected studies was scored independently by three reviewers (SdB, NV, CM) on the basis of six items adapted from two quality criteria lists [35,36] (Table 2). Our list included criteria that in our opinion were most relevant for studies on comprehensive care. The reviewers rated each criterion as ‘+’ (i.e. criterion fulfilled), ‘-’ (i.e. criterion not fulfilled), ‘?’ (i.e. lack of information) or ‘N.A.’ (i.e. not applicable). Since we did not use a complete standardized set of assessment criteria, we decided not to assign an overall quality rating per study. Hence, we only provide a total quality sum-score (ranging from 0 to 6) per study that was determined by counting the number of criteria scored positively. To draw conclusions regarding the effectiveness of comprehensive care programs, in line with earlier studies a best-evidence analysis was applied [37–39]. We distinguished four levels to rate the strength of evidence for each of the outcomes:

1. Strong evidence: consistent evidence for a beneficial effect of comprehensive care across multiple studies with high quality sum-scores;
2. Moderate evidence: consistent evidence for a beneficial effect of comprehensive care across multiple studies, including at least one study with a high quality sumscore and studies with lower quality sum-scores;
3. Insufficient evidence: inconsistent evidence for a beneficial effect of comprehensive care across multiple studies;
4. No evidence: only few studies available and/or consistent evidence for no effect of comprehensive care across multiple studies.

Similar to previous reviews that applied a best-evidence synthesis [37,38] results were considered consistent when at least 75% of the studies showed results in the same direction. Findings of studies with relatively higher quality sum-scores were valued more than findings of studies with relatively lower quality sum-scores.

3. RESULTS

3.1. Study retrieval

Our literature search yielded 3544 potentially relevant publications. On the basis of their title and abstract, 184 papers were selected by the reviewers to be retrieved fulltext for in-depth screening. This screening process resulted in 32 publications for inclusion in our study. The addition of 10 papers from our manual search resulted in a total of 42 publications that were classified as eligible for our review. Reasons for exclusion are shown in Fig. 1.

[FIGURE 1]

3.2. Study characteristics

3.2.1. Study designs and length of follow-up

The 42 included publications described 33 different studies i.e. fourteen randomized controlled trials, eight pretest-post-test studies, five controlled clinical trials, three cluster randomized controlled trials, two post-test only studies, and one case control study (Table 1). Across all studies, sample size varied from 25 to 65,132 subjects. Of the studies with a longitudinal design, twenty studies had a follow-up of ≤ 12 months and seven studies had a followup of >12 months. In three studies the length of follow-up was variable (e.g. depending on time to discharge).

3.2.2. Methodological quality of studies

None of the studies fulfilled all quality criteria (i.e. sum-score of 6) based on what could be retrieved from the information provided in the papers (Table 2). The observed minimum sum-score was 0 ($n = 6$) and the maximum sum-score was 5 ($n = 1$). The quality criteria “similar at baseline” and “drop-out rate” were most frequently scored positively. Only three papers reported enough information to assess the quality criterion regarding compliance [40–42]. The quality criteria “randomization”, “similarity at baseline”, “application of intention-to-treat-analysis”, and “adjustment for confounders” were not applicable for studies with a non-experimental design ($n = 11$).

[TABLE 1 AND TABLE 2]

3.2.3. Usual care conditions

In most studies ($n = 23$) the effects of comprehensive care programs were compared with those of care as usual (i.e. no comprehensive care). In twelve of these studies, the usual care conditions were not or only poorly described (Table 1). Usual care was mostly described as normal access to services available to frail older people, routine home, primary and hospital care, and/or encouragement to remain in care of their current physician.

3.3. Program characteristics

3.3.1. Target populations

The 33 different studies evaluated 28 different comprehensive care programs. The comprehensive care programs were implemented in the USA ($n = 17$), Canada ($n = 4$), Australia ($n = 3$), Italy ($n = 1$), Norway, ($n = 1$), United Kingdom ($n = 1$), and one program was implemented in both the Netherlands and the USA. Fifteen comprehensive care programs focused on frail people aged 65 years and older with multiple, not specified chronic conditions, functional disabilities, complex healthcare needs, and/or high use of healthcare services [11,43–64]. Seven programs focused on multimorbid older people who were (acutely) hospitalized and who sometimes had a history of readmissions or were at risk for readmissions [65–74]. Five programs focused on older people with (a combination of) specific chronic conditions such as

diabetes mellitus, heart failure, COPD, dementia and/or arthritis [40,42,75–79], and one program focused on people aged 50 years or older who were at risk of functional decline or physical deterioration [41] (Table 1).

3.3.2. *Settings*

The settings in which the comprehensive care programs were implemented varied from home care organizations and community centers to primary care practices, hospitals, specialized clinics (e.g. geriatric clinics and Veterans Affairs medical centers), and managed care organizations (Table 1). Consequently, the type of care that was provided also differed widely between the programs. Various comprehensive care programs incorporated a mix of care types, such as the Integrated Services for Frail Elders (SIPA) and the Nurse Physician Collaborative Partnership in Canada, the Integrated Community Care for Older People (ICCOP) in Australia, and the Health Enhancement Project (HEP) in the USA. These programs mostly included newly established partnerships between community centers, home care organizations, primary care practices, and/or hospitals [43,56,57,60]. Other programs enabled the provision of regular care services in settings in which they were not normally provided, such as the Older Hospitalized Patients' Discharge Planning and In-home Follow-up Protocol in Australia and the Geriatric Home Hospitalization Service in Italy both providing hospital care services at home [67,71].

3.3.3. *Contents*

Table 1 presents the contents of the comprehensive care programs included in our review. The table illustrates the diversity in the comprehensive care programs with regard to the number of included interventions and the number of related CCM components. We observed comprehensive care programs that included interventions related to two CCM components ($n = 5$), three CCM components ($n = 12$), four CCM components ($n = 3$), five CCM components ($n = 6$), and six CCM components ($n = 2$).

Except for one program [75], all comprehensive care programs included interventions related to the CCM component delivery system design. Examples are employing a case manager, working in multidisciplinary teams, designing individualized care plans, and making home visits to patients. The majority of comprehensive care programs ($n = 25$) additionally included interventions related to the CCM component self-management support, such as involving patients in the design of their care plan, educating patients to improve self-management, and stimulating patients to participate in self-management group sessions. Twenty comprehensive care programs included interventions related to the CCM component decision support. Interventions to support healthcare providers' decision-making included implementing evidence-based guidelines, training teams to implement new protocols, and supervising newly appointed case managers. Interventions related to the CCM components clinical information systems (e.g. feedback sheets, electronic patient records, and telehomecare units) and community resources (e.g. establishing access to community resources and partnerships with local community service centers) were less frequently observed ($n = 12$ for both components). A small

minority of the comprehensive care programs ($n = 4$) included interventions related to the CCM component health system. Examples of such interventions are installing committees to support new partnerships, employing management teams to support process and quality improvement, and enabling infrastructure for innovations in chronic care.

3.4. Impact of comprehensive care programs

Table 1 presents all outcomes reported in the studies included. Only outcomes that were reported in at least five studies are described in the text. More detailed information about the actual differences between comprehensive care groups and usual care groups or about actual changes over time for clinical outcomes are provided in Tables 3a and 3b, respectively. Quality of reporting on baseline and followup scores on the clinical patient outcomes widely varied across studies. deteriorated in the usual care group [79]. Two studies did not compare comprehensive care with usual care [55,60]. Mitton et al. [60] observed no significant change in cognitive functioning over time, whereas Duke et al. [55] suggested a deterioration of cognitive functioning over time. Considering these findings, there is no evidence for a beneficial effect of comprehensive care on cognitive functioning.

3.4.1.2. Depressive symptoms.

Seven studies measured the effect of comprehensive care on depressive symptoms of which three had relatively higher quality sumscores [50,56,58]. Five studies reported no differences between comprehensive care and usual care groups [50,56,61,68,76]. Two studies, however, reported a significantly larger reduction of depressive symptoms in the comprehensive care group than in the usual care group [58,66]. Considering these findings, there is no evidence for a beneficial effect of comprehensive care on depressive symptoms.

3.4.1.3. Functional status.

Nine studies evaluated the effects of comprehensive care on activities of daily living (ADL), of which three had relatively higher quality sum-scores [51,56,74]. Six studies reported no differences between comprehensive care and usual care groups [51,61,66,68,73,74]. Two studies reported a significantly larger improvement of ADL in the comprehensive care group compared to the usual care group [56,79]. Mitton et al. [60] presented the results of comprehensive care only, showing no effects on ADL.

[TABLE 3]

The effect of comprehensive care on instrumental activities of daily living (IADL) was evaluated in six studies, of which one had a relatively higher quality sum-score [51]. Five studies observed no effect of comprehensive care on IADL [51,61,66,68,73] while one study observed significant improvement of IADL in the comprehensive care group and significant deterioration in the usual care group [79]. Frequency of falls was evaluated in two studies [50,61]. Both studies found no difference between the effect of comprehensive care and usual care. One study

evaluated the effect of comprehensive care on physical performance and reported no effect of comprehensive care [56].

Considering these findings, there is no evidence for a beneficial effect of comprehensive care on functional status.

3.4.1.4. Health behavior.

Health behavior, including physical activity, dietary habits, and immunization compliance, was evaluated in five studies. Overall, quality sum-scores of these studies were low. One study observed that health behavior (i.e. exercise) improved significantly more in the comprehensive care group than in the usual care group [56], whereas one study found no effect of comprehensive care on health behavior (i.e. exercise and cognitive symptom management) [77]. The studies that did not compare comprehensive care with usual care found a (significant) improvement of behavior towards, diet, exercise, immunization or medication but not towards cognitive symptom management [40,64,78]. Considering these findings, there is moderate evidence for a beneficial effect of comprehensive care on health behavior.

3.4.1.5. Health-related quality of life.

Effectiveness of comprehensive care regarding health-related quality of life was reported in seventeen studies including six with relatively higher quality sum-scores [50,51,56,58,67,74]. Studies differed widely in the definition and measurement of health-related quality of life. Thirteen studies compared health-related quality of life between patients receiving comprehensive care and patients receiving usual care. Nine of these studies reported no differences between comprehensive care and usual care groups [40,50,56,61,65,73,74,76,77]. Two studies reported that comprehensive care favored usual care in terms of mental functioning but not in terms of physical functioning [51,58]. Courtney et al. [67] observed that comprehensive care favored usual care in terms of mental as well as in terms of physical functioning. Also Zhang et al. [75] observed for the majority of aspects of quality of life a significant effect of comprehensive care (i.e. significantly slower deterioration than in the usual care group). Four studies did not compare comprehensive care with usual care [55,60,64,78], with two studies observing an improvement in quality of life over time due to comprehensive care [55,64]. Considering the inconsistent findings across studies, there is insufficient evidence for a beneficial effect of comprehensive care on quality of life in terms of mental functioning. Almost none of the studies, including those with relatively higher quality sum-scores, reported positive effects of comprehensive care on health-related quality of life in terms of physical functioning. Considering these findings, there is no evidence for a beneficial effect of comprehensive care on quality of life in terms of physical functioning.

3.4.1.6. Medication use.

Six studies evaluated the effect of comprehensive care on medication use. Most of these studies had relatively low quality sum-scores. Two studies found no differences between comprehensive care and usual care groups [50,66]. Three studies, however, observed that comprehensive care favored usual care in terms of medication

compliance, medication appropriateness, antipsychotic and unnecessary drug use, detection of adverse drug reactions, and conditions with omitted drugs [40,70,71]. One study did not compare comprehensive care with usual care but also reported an improvement in medication management due to comprehensive care [62]. Considering the inconsistent findings across studies, there is insufficient evidence for a beneficial effect of comprehensive care on medication use.

3.4.1.7. Mortality.

Mortality was evaluated in six studies (Table 3b) [51,54,69,71,73,74], of which most had relatively low quality sum-scores. Two of these studies found a significantly lower mortality rate and/or a significantly longer time to death in the comprehensive care group than in the usual care group [54,74]. In one of these studies, however, this effect was only observed for a subgroup of patients with complex diseases including diabetes mellitus [54]. Considering the fact that almost none of the studies, including those with relatively higher quality sumscores, reported positive effects of comprehensive care on mortality, there is no evidence for a beneficial effect of comprehensive care on mortality.

3.4.1.8. Perceived quality of care and satisfaction.

Fourteen studies measured perceived quality of care and patient satisfaction. Five studies compared effects of comprehensive care and usual care [44,48,50,51,74]. Four had relatively high quality sum-scores. Two studies found significantly higher perceived quality of care or satisfaction with care in the comprehensive care group than in the usual care group [44,74]. Two studies observed no differences between comprehensive care and usual care groups [50,51]. One study found that comprehensive care favored usual care for some aspects of care (e.g. quality of patient-physician communication) whereas for other aspects no differences were found (e.g. physician's knowledge of patient, quality of integration of care, trust in physician) [48].

Nine studies only reported outcomes for patients receiving comprehensive care and found that the majority of patients were satisfied with the program. Patients found the comprehensive care program helpful and user-friendly, and appreciated the holistic approach. They further believed that the program helped them to manage their disease, had improved their health, and made it easier to get access to healthcare services [11,40–42,60,62,64,76,77]. Considering the fact that two studies with relatively high quality sum-scores reported positive effects of comprehensive care on quality of care and satisfaction and that these findings were supported by qualitative findings, there is moderate evidence for a beneficial effect of comprehensive care on quality of care and patient satisfaction.

3.4.2. Patient related outcomes—economic outcomes

3.4.2.1. Healthcare utilization and healthcare costs.

Twentyfive studies evaluated the effect of comprehensive care on healthcare utilization and/or healthcare costs (Table 1). We distinguish the effect on inpatient

healthcare utilization and outpatient healthcare utilization. Twenty-one studies measured the utilization of inpatient healthcare services.

Sixteen studies compared inpatient healthcare utilization between patients receiving comprehensive care and patients receiving usual care, including seven with relatively high quality sum-scores [43,46,50,52,56,67,74]. Studies differed widely in the definition and measurement of utilization of inpatient healthcare services (e.g. number of ER visits, hospital readmission rate, length of hospital stay, number of hospitalizations, and percentage of patients using nursing home care).

Comprehensive care favored usual care in six studies [51,56,67,72,74,75]. In two of these studies the ER visit rate was significantly lower in the comprehensive care group than in the usual care group [51,75]. In three studies the number of hospital (re)admissions was significantly lower and/or the time to readmission significantly longer in the comprehensive care group than in the usual care group [67,74,75]. In one study length of hospital stay significantly decreased in the comprehensive care group whereas it significantly increased in the usual care group [56]. Two studies observed significant differences between comprehensive care and usual care groups that were not in favor of comprehensive care [43,54]. One of these studies found significantly more ER visits in the comprehensive care group than in the usual care group [54]. The other study found significantly higher utilization of nursing home care in the comprehensive care group than in the usual care group [43]. No significant differences were observed for other parameters measured in these studies. Eight studies that compared utilization of inpatient healthcare services between patients receiving comprehensive care and patients receiving usual care observed no significant differences between the groups for any of the parameters that were measured [40,46,49,50,61,65,66,76]. Although differences in the utilization of inpatient healthcare services were mostly not significant, five studies that also measured healthcare costs, reported negative incremental direct healthcare costs (i.e. lower direct healthcare costs for patients receiving comprehensive care than for patients receiving usual care). Across these studies, of which four had relatively high quality sum-scores [43,46,50,74], incremental healthcare costs ranged from $-\$5708$ to $-\$204$ per patient per year [43,46,49,50,74]. This was primarily due to lower inpatient healthcare costs in the comprehensive care group than in the usual care group.

Five of the twenty-one studies that measured utilization of inpatient healthcare services did not compare comprehensive care with usual care [42,55,57,60,78]. One of these studies reported no significant change over time in ER visits, hospitalizations, and length of hospital stay [78]. In the other studies change over time was not tested for significance. These studies, however, observed reductions in the use of hospital care and ER visits. Reductions in hospitalizations varied from 38% to 69% [42,55,60]. Reductions in the length of hospital stay varied from 37% to 64% [55,57,60]. Reductions in the number of ER visits ranged from 32% to 54% [55,57,60]. These findings are in line with the findings of the studies that reported direct inpatient healthcare costs for the comprehensive care group only [11,55,60,63,72,75]. Two of these studies reported cost savings ranging from $\$3029$ to $\$6198$ per patient per year. These savings were primarily due to less hospitalizations and ER visits, and reduced length of hospital stay during (re)admission [60,72]. Four other studies that only reported direct healthcare costs for the comprehensive care group reported cost reductions due to comprehensive care

ranging from \$147,000 to \$1.8 million per year for patients included in the study which again were primarily due to significant reduced numbers of ER visits and hospitalizations or a reduced length of hospital stay [11,55,63,75].

Six studies measured utilization of outpatient healthcare services [40,43,46,56,65,76], of which three had relatively high quality sum-scores [43,46,56]. All studies compared comprehensive care with usual care. Béland et al. [43] observed significantly more GP visits, home care visits, and visits to day hospitals in the comprehensive care group than in the usual care group. This resulted in significantly higher outpatient healthcare costs in the comprehensive care group than in the usual care group. These findings are supported by the study that reported positive incremental healthcare costs of \$1321 per patient per year (i.e. higher healthcare costs in the comprehensive care group) [52]. In this study, costs for chronic (including comprehensive care) and preventive care were significantly higher in the comprehensive care group. Leveille et al. [56] observed significantly higher senior centre participation in the comprehensive care group than in the usual care group, whereas Kobb et al. [40] observed significantly less outpatient and pharmacy visits in the comprehensive care group than in the usual care group. Four studies observed no differences in utilization of (other) outpatient healthcare services between comprehensive care and usual care groups [46,56,65,76].

Two studies did not specify costs for inpatient and outpatient healthcare services [58,64]. One study compared healthcare costs of the comprehensive care group with these of the usual care group, and found no effect of comprehensive care [58]. The other study reported only healthcare costs for the comprehensive care group and observed that the actual healthcare costs were significantly lower than the projected healthcare costs [64].

Although quality sum-scores and findings differed across studies, there were six studies with relatively high quality scores and five studies with relatively lower quality scores that reported decreased inpatient healthcare utilization and/or decreased healthcare costs due to comprehensive care. Based on these findings, there is moderate evidence for a beneficial effect of comprehensive care on inpatient healthcare utilization and healthcare costs. Two studies with relatively high quality sum-scores observed higher outpatient healthcare utilization due to comprehensive care groups. These findings were, however, not supported by the studies with relatively lower quality sum-scores. Moreover, the four studies that observed differences between comprehensive care and usual care groups widely differed in the measurement of utilization of outpatient healthcare services. Considering these findings, there is insufficient evidence for an effect of comprehensive care on outpatient healthcare utilization.

3.4.3. Informal caregiver related outcomes

Six studies reported the effect of comprehensive care on informal caregivers. Outcomes varied from depressive symptoms and caregiver strain to caregiver's productivity loss, satisfaction, and perceived quality of care. Two studies compared effects of comprehensive care with usual care [47,71]. Quality sum-scores of these studies were rather low. One of these studies reported significantly higher perceived quality of care in caregivers of patients enrolled in a comprehensive care program than in those of patients that received usual care, but found no effect of comprehensive care on caregiver depression, caregiver strain, and productivity loss

[47]. Tibaldi et al. [71], however, observed a significantly larger reduction of caregiver strain in caregivers of patients that received comprehensive care than in caregivers of patients that received usual care. Considering these findings, there is no evidence for a beneficial effect of comprehensive care on caregiver burden. Four studies only reported outcomes for caregivers of patients that received comprehensive care and observed that caregivers were satisfied with the program [41,60], experienced an improved ability to cope with the disease of their family member, and experienced less anxiety and caregiver burden [42,60,62]. Although quality sum-scores of these studies were rather low, these studies' findings were rather consistent. Considering these findings, there is moderate evidence for a beneficial effect of comprehensive care on satisfaction of informal caregivers.

3.4.4. Professional caregiver related outcomes

Nine studies reported the effect of comprehensive care on professional caregivers. Outcomes varied from satisfaction and knowledge to experiences with processes of care. Two studies compared outcomes of caregivers providing comprehensive care with those of caregivers providing usual care [45,59]. Quality sum-scores of these studies were relatively low. Both studies observed that caregivers providing comprehensive care were significantly more satisfied with communication with patients and family members and some aspects of their knowledge than caregivers providing usual care. They did not report any differences in time spent on patient care and care coordination.

Seven studies only reported outcomes for caregivers providing comprehensive care and observed that the majority of caregivers expressed high levels of satisfaction with e.g. communication with other healthcare providers and newly established partnerships. They further indicated to be better able to meet the needs of frail older patients and that the program decreased time spent on patient care [11,40,41,50,60,76]. One study suggested that comprehensive care enabled early detection and treatment of problems [42]. Although quality sum-scores of the two studies that compared outcomes of caregivers providing comprehensive care with those of caregivers providing usual care were rather low, their findings were in line with the qualitative findings of the other studies. Considering these findings, there is moderate evidence for a beneficial effect of comprehensive care on satisfaction of professional caregivers.

4. DISCUSSION

This systematic literature review summarizes available information about the characteristics of comprehensive care programs for people with multiple chronic conditions and about their impact on patients and caregivers. There is a vast amount of literature on comprehensive care. However, most literature focuses on comprehensive care programs for people with a single disease [e.g. 19,29–31,82,83–85]. Our work focuses on comprehensive care programs for people with multiple diseases, and therefore adds to the current literature. Research on multimorbidity is still in its infancy [6,14,75]. With this review we therefore aimed to contribute to a scientific basis for the improvement of care for patients with multimorbidity.

We conducted a thorough systematic review of thirty-three studies that examined twenty-eight different comprehensive care programs for multimorbid patients. Although our study includes more recent studies than earlier review studies on the same subject [17,20–25], evidence regarding the effectiveness of comprehensive care remains inconsistent. Overall, the effects of comprehensive care were comparable to or more positive than those of usual care. Moderate evidence was found for a beneficial effect of comprehensive care on inpatient healthcare utilization and healthcare costs. Moderate evidence was also found for a beneficial effect of comprehensive care on health behavior of patients, perceived quality of care, and satisfaction of patients and caregivers. Insufficient evidence was found for a beneficial effect of comprehensive care on health-related quality of life in terms of mental functioning, medication use, and outpatient healthcare utilization and healthcare costs. No evidence was found for a beneficial effect of comprehensive care on cognitive functioning, depressive symptoms, functional status, mortality, quality of life in terms of physical functioning, and caregiver burden.

The majority of comprehensive care programs incorporated interventions related to three or more CCM components. As observed in recent studies on comprehensive care programs for people with a single disease [27–30,86], also almost all comprehensive care programs for people with multiple chronic diseases included interventions related to the CCM components delivery system design and self-management support. In contrast to these studies, however, several programs reviewed in our study included interventions promoting access to community resources. Such interventions were particularly part of the programs for frail older people and were mostly designed as partnerships between primary care practices or hospitals and local community service centres to establish easy access to community resources (e.g. transportation, meals, and adult day care) for patients and assessment of patient needs regarding community services [e.g. 43,45,53,56,60]. This may well reflect an increasing attention for social issues of multimorbid patients. This is an important finding since the integration of medical and social services is advocated to optimize care for patients with multiple chronic conditions [11,87].

The diversity in the effects of comprehensive care programs may be related to the substantial variation in the programs in terms of target patient groups, design of the intervention/program, and settings in which they were implemented. It is hard to determine to which program components positive effects could be attributed and under which circumstances comprehensive care programs may be most effective.

The diversity in the effects of comprehensive care programs may also be related to whether the programs were correctly implemented, whether the program components were integrated, and whether they were fully adopted by the patients and the caregivers involved. The level of implementation of the comprehensive care programs was discussed in few studies only. Explanations proposed for a lack of positive effects of comprehensive care were inadequate integration of newly developed interventions in daily practice, insufficient understanding of the care innovations among caregivers involved, inadequate skills for implementing the innovations, insufficient time to adapt to newly implemented care models, and non-compliance of patients [43,51,65,67].

Finally, the wide variety in the study results may also be related to differences in usual care conditions. Our study yielded comprehensive care programs from seven countries. As was also suggested in studies on comprehensive care programs for

patients with a single-disease [83,88], differences in healthcare systems between countries and between settings within countries, and differences in usual care settings are to be expected. Information about the usual care conditions tended to be poor, which made it hard to distinguish the usual care conditions from the comprehensive care conditions. Consequently, it is often not possible to determine whether differences in study results could be related to differences in comprehensive care programs or to differences between comprehensive care and usual care.

Although our study provided insight into the characteristics of a large number of available programs for multimorbid patients and into their potential effects, we should acknowledge its limitations. A limitation of our search strategy is that we included scientific papers written in the English language only. Therefore, we may have missed relevant comprehensive care programs.

Another limitation was that we could not use a complete standardized tool to assess the methodological quality of the included studies. The usefulness and relevance of existing assessment instruments are limited as several of the quality assessment criteria are not applicable to studies on comprehensive care [89]. Also the Health Technology Assessment—Disease Management (HTA-DM) instrument [89] which was specifically developed to assess the quality of complex interventions such as comprehensive care has limitations and needs further validation [28,90]. We therefore decided to select six criteria from existing quality criteria lists [35,36] that in our opinion were most relevant for the assessment of studies on comprehensive care programs. With this approach, we aimed to provide some insight into the quality of the included studies and into the strength of evidence. Quality assessment was sometimes, however, hampered by poor or lacking information in the papers.

Furthermore, four quality criteria did not apply to studies with non-experimental study designs. Consequently, these studies have been assigned lower quality sum-scores, suggesting lower study quality, which may not be justifiable. It should further be noted that our study did not only aim to determine the effectiveness of comprehensive care programs but also to determine the characteristics of comprehensive care programs. Like papers describing studies with higher quality sum-scores, the papers describing studies with relatively lower quality sum-scores could therefore also provide relevant information regarding the characteristics of comprehensive care programs.

The consequences of including studies irrespective of their methodological quality were that we observed variation in study designs and length of follow-up. Moreover, we observed a wide variety in outcome measurements and how they were made operational, and a high rate of missing data (e.g. standard deviations for mean values). These issues are generally acknowledged by researchers investigating comprehensive care [21–23,91–93]. Against this backdrop we considered estimating an average effect of comprehensive care by means of meta-analysis of little value. Hence, we limited ourselves to qualitative comparisons of the results of the included studies. It was further hard to determine which number of CCM components and which combinations are most promising.

These findings are not unique to comprehensive care programs for patients with multiple chronic conditions. Likewise, recent studies focusing on comprehensive care programs for people with a single-disease suggest that it is hard to determine to which number and to which components positive effects of comprehensive care can be attributed [27,30,31,84]. A study focusing on programs with a single-disease

approach suggests that programs that contain interventions related to at least one CCM component improve clinical outcomes and processes of care [29]. For COPD patients significant effects on hospitalizations and ER visits have been found for programs that contained interventions related to at least two CCM components [28,31]. For other outcomes or in other studies focusing on comprehensive care programs for COPD patients it was observed that programs should include interventions that related to at least three or even four CCM components to be effective [28,93].

Also with regard to the type of CCM components mixed results have been reported. Some studies suggest that the CCM components self-management support, delivery system design, and decision support are associated with better clinical outcomes and/or processes of care [29,30]. Another study, however, failed to find an association between the elements self-management support or delivery system design and clinical outcomes [94]. The CCM has, however, been promoted as a unified package; the different CCM components are supposed to have a synergistic effect in which the whole is greater than the sum of the parts [29,84].

The finding that comprehensive care programs may be effective in terms of reducing healthcare utilization and as a result in reducing healthcare costs is promising. The increasing prevalence of chronic diseases has major economic consequences for healthcare systems, and it is therefore important to have insight into strategies that may reduce healthcare costs. However, comprehensive care programs are not only implemented to make efficient use of healthcare resources, but also to improve patient health outcomes. In line with other recent studies, we found hardly any studies that suggested a positive effect of comprehensive care on clinical patient outcomes (i.e. cognition, depressive symptoms, functional status, mortality). An important explanation for this finding, which was also suggested by others [21], may be that multimorbid patients are too a heterogeneous group with large variations in the progression of their diseases and impairments. Conditions may be too severe to be affected by the interventions offered and the time too short to establish an effect [51,95,96]. Moreover, in most studies standardized assessment tools were used to evaluate effects of comprehensive care on patient health outcomes. It has been suggested that such instruments are not sufficiently sensitive to capture clinically important changes over time that can be attributed to comprehensive care programs [97,98].

To support decision-making in the field of chronic care for patients with multiple chronic conditions, it is necessary to enhance comparability between studies. It is therefore recommended to better describe the comprehensive care programs, their level of implementation, and the usual care conditions to which their effectiveness is compared. Only then more consistent evidence for their effectiveness may be obtained. Since there are indications that comprehensive care for patients with multiple chronic conditions may be cost-saving, it is further recommended to perform more rigorous economic evaluations that include similar cost dimensions and take both costs and effects of comprehensive care into account. Our study revealed substantial variation in the costs that were taken into account in the included studies (e.g. inpatient costs, outpatient costs, costs of comprehensive care program), which hampers comparability of their results. Insight into the economic effects of comprehensive care, in particular the incremental costs of the programs, are of

primary interest, since they provide information about the potential added value of comprehensive care as compared to usual care.

In addition, more insight is needed into the impact of comprehensive care on caregiver burden. Literature suggests that caregiver burden is a predictor of institutionalization of frail older people, particularly those with dementia [99]. Older people are increasingly stimulated to live independently for as long as possible. Future studies should therefore examine the effect of comprehensive care on predictors of institutionalization, such as caregiver burden, to be able to establish whether comprehensive care programs may delay or prevent institutionalization. It is further recommended to gain more insight into patient and caregiver satisfaction, and perceived quality of care. Most studies included in this review measured these outcomes only after the implementation of the comprehensive care program and did not compare these outcomes with (family caregivers of) patients receiving usual care and professional caregivers providing usual care. It is therefore recommended to measure satisfaction and perceived quality of care both before and after the implementation of the comprehensive care program and thus be able to determine the effect of comprehensive care. Such information is valuable since it may provide insight into processes underlying positive or negative outcomes of care.

Finally, in line with the client-centered approach in healthcare it is recommended to incorporate individual goals and individual preferences and needs in the evaluation of comprehensive care programs for multimorbid patients. Such methods (e.g. Goal Attainment Scaling) may be more meaningful and more sensitive to detect clinically important change related to comprehensive care than standard assessment tools that are mostly used [97,98].

5. CONCLUSION

There is a broad array of comprehensive care programs available to patients with multiple chronic conditions that often integrate both medical and social services. Despite indications that comprehensive care programs for multimorbid patients decrease inpatient healthcare utilization and healthcare costs, improve health behavior of patients and perceived quality of care, and realize satisfaction of patients and caregivers because of the heterogeneity of the programs it is as yet too early to draw firm conclusions regarding their effectiveness. It remains hard to determine which patient groups benefit most from comprehensive care and which program characteristics contribute most to positive effects of comprehensive care. More consistently performed evaluation studies are necessary to determine what constitutes best care for the increasing number of people with multiple chronic conditions.

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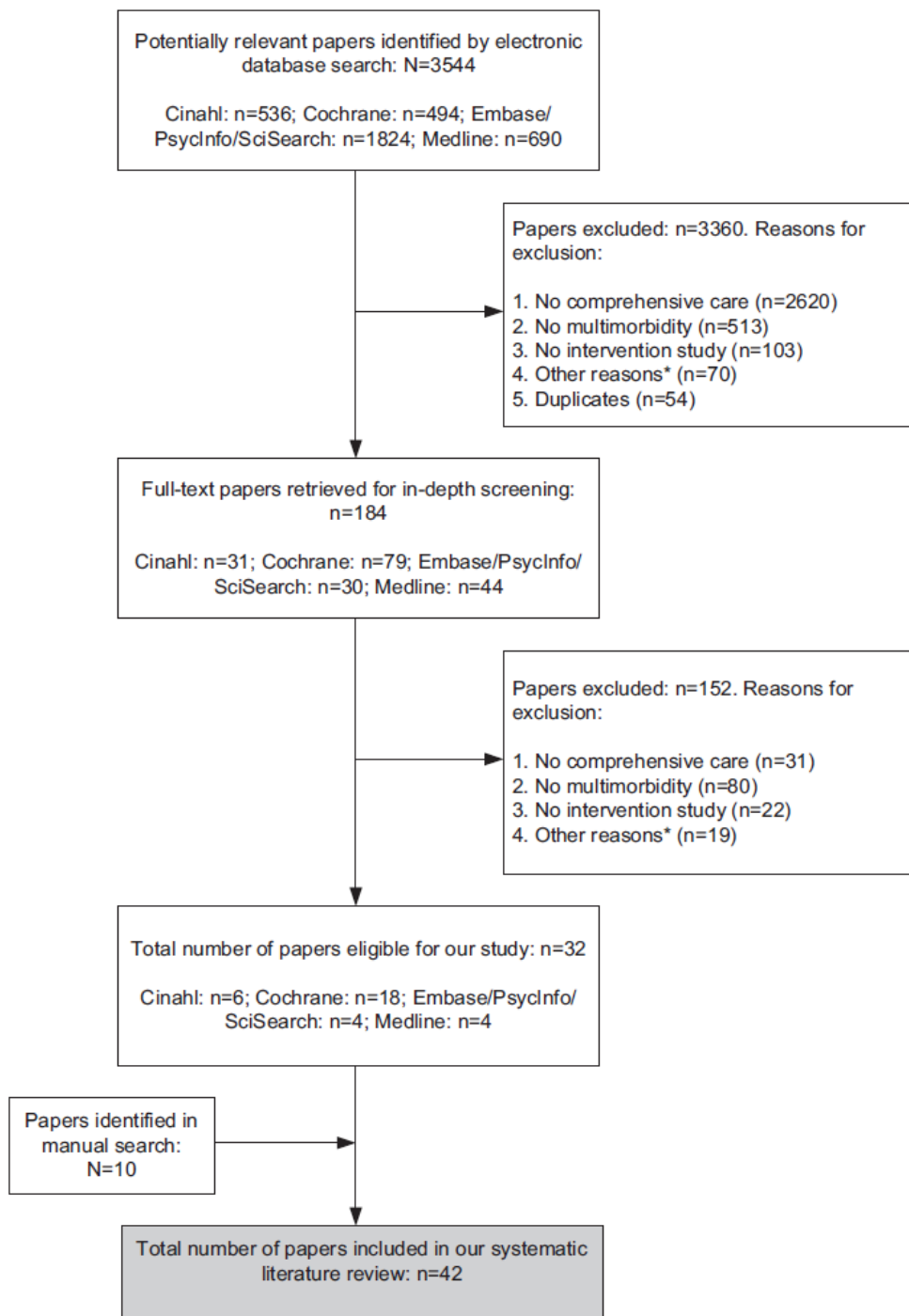
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TABLES

Fig. 1. Flow diagram of literature screening process.



*e.g. papers were not written in English, papers could not be retrieved, identified documents were non-scientific papers, papers described the design of an intervention study only.

Table 1
Characteristics and outcomes of studies evaluating the impact of comprehensive care programs for multimorbid patients.

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Anonymous [63]	Pretest-posttest design (pilot) (N=60)	12	Highly complex patients with about 7 diagnoses and high healthcare consumption.	Hospital care, community care, and home care in the USA	Enhanced Care Initiatives (ECI) CR: coordination of transportation, meals, and other support services in the community. DS: ECI for physicians in case of questions or concerns. DSD: home visit by nurse for initial geriatric assessment, then weekly or biweekly contact and sometimes daily contact; physicians are regularly informed about patients; nurse accompanies patient to physician. HS: fee for physicians for their time and cooperation with the program. SMS: group sessions at a community center for education, exercise, and entertainment; nurse gives education, reviews and upgrades dietary choices, suggests home safety improvements, and implements an exercise program tailored to the patients needs.	N.A.	Patients Inpatient and outpatient hospital expenditures decreased considerably (i.e. \$265,085) after implementation of the program (change over time was not tested for significance).
Béland et al. [43]	RCT (N = 1309)	22	Frail older people aged ≥65 years with functional disabilities and complex service needs and their informal caregivers.	Community, primary, and hospital care by Integrated Services for Frail Elders (SIPA) sites (located within local community service centers) in Canada	Integrated Services for Frail Elders (SIPA) CIS: development of SIPA system to monitor performance of team with regard to administrative procedures and services received by patients. CR: partnership with local community service centers to rapidly mobilize community based services. DS: design of interdisciplinary intervention protocols and service delivery processes based on the latest knowledge and adapted to local population; SIPA training for all personnel. DSD: responsibility of SIPA site for the delivery of all services, including health and social, acute and long-term, and community and institutional care; supervision of SIPA by program director being responsible for clinical staff; integrated health and social services offered under responsibility of a case manager and a multidisciplinary team; regular adaptation of intervention plans including services to be provided to patients' circumstances and needs; 24/7 on-call services. HS: SIPA sites clinically and financially independent; system based on community primary care services (health and social, acute and long-term, and community and institutional, including acute care hospitals and nursing homes); system created to assess quality of services and management on ongoing basis; implementation of changes in clinical, organizational, and management practices; development of inter-organizational agreements (e.g. shared clinical responsibility); installation of committees to support team and patients (regional, site monitoring, inter-site coordination, and working committee). SMS: involvement of patients and caregivers in care planning.	Usual services available to frail older people.	Patients Average total healthcare costs per patient during the study did not differ significantly between groups; 1. costs for community services were significantly higher for intervention than for control group; 2. costs for institutional services were significantly lower for intervention than for control group. Incremental healthcare costs were ~\$204 per patient per year. Utilization of home care and GP services, and number of hours nursing home care during the study were significantly higher in intervention than in control group. Utilization of specialist care, prescribed drugs, number of days in acute care, number of days in long-term acute care, number of days in nursing homes, number of hours of social services, and number of hours at ER during the study did not differ significantly between groups. % of patients with long-term stay was significantly lower during the study in intervention than in control group. % of patients accessing acute and ER care and who were institutionalized did not differ significantly between groups.

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Boult et al. [45]; Boyd et al. [44]; Leff et al. [46]; Wolff et al. [47]	cRCT (N=904 patients; N=308 informal caregivers; N=33 professional caregivers)	8 (healthcare costs and utilization), 12 (professional caregivers), and 18 (other patient outcomes and informal caregivers)	Multimorbid people aged ≥65 years with high probability of using health services intensively/at high risk for incurring high healthcare costs in the coming year.	Primary care by 8 primary care practices in the USA	Guided Care (GC): integrating registered nurse (GC nurse) into primary care practice to collaborate with 2-5 physicians in providing comprehensive care to 50-60 patients. CIS: clinical processes provided by GC nurse are guided by web-accessible electronic health records. CR: establishing access to community resources for patients by GC nurse. DS: education for GC nurses to provide comprehensive care; clinical processes provided by GC nurse are guided by scientific evidence. DSD: comprehensive assessment at home; development care plan; monthly monitoring; support transitions into and out of hospitals; coordination of all providers of care by GC nurse. SMS: involvement of patient in development self-care plan; referral to self-management course; coaching for self-management; education and support of family caregivers by GC nurse.	N.R.	Patients Mean annual healthcare costs and healthcare utilization (i.e. hospital admissions, hospital days, skilled nursing facility admissions, skilled nursing facility days, ER visits, GP visits, specialist visits, home healthcare) during the study did not differ significantly between groups. Incremental healthcare costs were ~\$1394 per patient per year. Perceived quality of care at follow-up was significantly higher in intervention than in control group; 1. mean overall quality of care score, and mean goal setting, coordination of care, problem solving, and patient activation sub scores were significantly higher in intervention than in control group; 2. intervention group was significantly (1.5-2 times) more likely than control group to rate their overall quality of care, decision support, and coordination of care as "high-quality". Mean decision support sub score and rating of goal setting, problem solving, and patient activation at follow-up did not differ significantly between groups. Patients in intervention group that rated baseline quality of care as "low" were significantly (twice) more likely to rate their overall quality of care at follow-up as "medium or high". Informal caregivers Caregiver depression and caregiver strain at follow-up did not differ significantly between groups. Perceived quality of care at follow-up was significantly higher in caregivers of patients receiving GC than of those receiving usual care. Caregivers reported significantly higher quality for 4 out of 5 subscales: goal setting, coordination of care, decision support, and patient activation. Perceived quality of care for problem solving did not differ significantly between groups. Productivity loss in terms of regular activity and work productivity at follow-up did not differ significantly between caregivers from both groups.

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Boyd et al. [48] and Sylvia et al. [49]	CCT (pilot) (N=150)	6	Multimorbid people aged ≥65 years and with high probability of using health services intensively in the coming year.	Primary care by 1 primary care practice in the USA	Guided Care (see Boulton et al. [45])	N.R.	<p>Professional caregivers</p> <p>Over time, physicians providing guided care significantly more improved their satisfaction with 5 out of 11 aspects of care (i.e. communication with patients, communication with family caregivers, education of family caregivers, motivation of patients, and referral to community resources) and with 1 out of 6 aspects of knowledge (i.e. knowledge of medications patients are taking) than physicians providing care as usual.</p> <p>Change in rating of provider team's problem-solving performance, patient activation, other aspects of knowledge, time spent on patient care, and care coordination over time did not differ significantly between physicians from both groups.</p> <p>Patients</p> <p>Healthcare costs and healthcare utilization (i.e. hospital admissions, hospital days, ER visits, primary care visits) did not differ significantly between groups during the study. Incremental healthcare costs were -\$3089 per patient per year.</p> <p>Change in quality of patient-physician communication over time differed significantly between intervention group and control group: quality of patient-physician communication significantly improved in intervention group.</p> <p>Change in physician's comprehensive knowledge of patient, quality of integration of care, interpersonal treatment, and trust in physician over time did not differ significantly between groups.</p>
Brand et al. [65]	CCT (N=106)	3 and 6	General medical patients aged ≥65 years with an inpatient stay of >24 hours and with either a history of admissions to acute care, multiple medical co-morbidities, or admission diagnosis of CHF.	Hospital care by 1 tertiary teaching hospital in Australia	Transitional care service model. CR: within 2 weeks after discharge (if necessary) coordination of community services by chronic disease nurse consultant (CDNC). DSD: consult patient with CDNC within 24 hours before discharge from hospital (pre-discharge data, screening risk factors for readmission, liaison with discharge planners, nursing staff and allied health staff, inform GP about patient's discharge); consult patient with CDNC in chronic care clinic within 2 weeks after discharge (evaluate patient's health status, medication, inform patient's GP, coordination of liaison between CDNC and GP, organization of home visiting). SMS: development of follow-up and action plan (at discharge) and review of action plan (within 2 weeks after discharge) by CDNC and patient, addressing self-management and social issues within 2 weeks after discharge by CDNC.	Medical, nursing and allied health intervention consistent with the patient's diagnosis and resources available on the general medical wards. Also includes discharge planning by the multidisciplinary team and could include out-patient follow-up.	<p>Patients</p> <p>GP visits and quality of life at 3-month follow-up did not differ significantly between groups.</p> <p>ER visits and readmission rate at 6-month follow-up did not differ significantly between groups.</p>

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Burns et al. [66]	RCT (N=130)	12	Hospitalized veterans aged ≥65 years diagnosed with ≥1 ADL deficit, ≥2 chronic medical conditions, ≥2 acute hospitalizations in previous year, or taking ≥6 scheduled prescription drugs.	Hospital care by Veterans Affairs medical center in the USA.	Outpatient Geriatric Evaluation and Management (GEM) clinic. DS: participation of interdisciplinary team in extensive team training and development. DSD: interdisciplinary primary care team (geriatric physicians, nurse practitioner, social worker, psychologists, clinical pharmacists) that focused on evaluation and long-term management or primary care (particular focus on special elderly problems); review by team of patients' and caregivers' resources and needs; initial 2-hour assessment was performed by entire team; team developed goals, interventions, and treatment and provided continuous individualized follow-up and aftercare after discharge (e.g. short-term hospital admission, routine care in clinic by relevant healthcare providers with telephone follow-up).	After hospital discharge inpatient treatment team referred patients back to previous provider(s) or to new provider(s) if necessary. Outpatient care was provided in ambulatory care clinics of the VA medical center or by local physicians in the community.	<p>Patients</p> <p>Overall, ADL deteriorated significantly over time but did not differ significantly between groups.</p> <p>Overall, cognition and IADL improved significantly over time but did not differ significantly between groups.</p> <p>Overall, depressive symptoms and health perception were significantly less and higher, respectively in intervention than in control group, and change over time differed significantly between the groups in favor of the intervention group.</p> <p>Overall, the number of hospitalizations increased significantly over time, but did not differ significantly between groups.</p> <p>Overall, life satisfaction did not differ significantly between groups and did not change significantly over time. However, change over time differed significantly between groups, in favor of the intervention group.</p> <p>Overall, the number of medications during the study was significantly lower in intervention than in control group, but change in the number of medications over time did not differ significantly between groups.</p> <p>Overall, social activity was significantly higher in intervention than in control group, and change over time differed significantly between groups in favor of the intervention group.</p>

Chumbler et al. [79]	Case control design in which subjects receiving comprehensive care were compared with subjects from another longitudinal study (N = 226)	12	Veterans with, hypertension, congestive heart failure, respiratory disease, or diabetes, who had >2 ED visits, hospitalizations, or unscheduled walk-in visits in the previous 12 months, and/or obtained care costing >\$25,000.	Home care by Veterans Health System in the USA	Rural Home Care Project (RHCP) CIS: each patient was given one of three types of home-telehealth with communication opportunities: 1. hand-held in-home messaging device (called Health Buddy) with disease management dialogues; monitoring of health status of patients by care coordinators on daily basis with interactive sessions (\pm 30 minutes) to determine risk of health-care crises; 2. telemonitor with two-way audio video connectivity allowing biometric monitoring; care coordinators assess patients in weekly sessions (15-20 minutes); 3. videophone with two-way audio video connectivity without biometric monitoring; assessment of patients by care coordinators in weekly sessions (15-20 minutes). appropriate system was selected by RHCP team to meet specific patient needs and to enhance effectiveness of care coordinator. DS: decision tree for selecting most appropriate system. DSD: provision of care by RHCP team (i.e. geriatric nurse practitioners, social worker, program support assistant); pro-active management of patients by care coordinators to prevent ER-visits and hospital admissions. SMS: education of all patients by care coordinators on chronic disease; encouragement of self-management behavior (e.g. to prevent health crises); enhancement of communication between patient and health-care system.	Disabled elders \geq 60 years, with \geq 1 (IADL) limitation recruited from another longitudinal study.	Patients With the exception of change in cognitive functioning measured with the MMSE change over time in all outcomes differed significantly between the groups, in favor of the intervention group. IADL and cognitive functioning measured on FIM cognitive subscale improved significantly over time in intervention group and significantly deteriorated in the control group. ADL, cognitive functioning measured with the MMSE, and independent functioning significantly improved in the intervention group and remained stable in the control group.
Coleman et al. [50]	RCT (N = 169)	24	Frail older adults aged \geq 65 years at high risk for hospitalization and functional decline in the subsequent 4 years.	Primary care by 9 primary care physician practices in the USA	Chronic care clinics DS: training to physician and nurses in population-based medicine and management strategies (geriatric syndromes); on-the-job coaching of nurses by study staff. DSD: 3-4 monthly visits to primary care practice for development of shared treatment plan by physician and nurse; session with pharmacist about polypharmacy and medications associated with functional decline; health status assessment. SMS: 3-4 monthly visits to primary care practice for self-management group session led by nurse or social worker.	N.R.	Patients No significant differences between intervention and control group in depressive symptoms, proportion of patients reporting falling in the past year, health-related quality of life (physical functioning), urinary incontinence, and rate of use of high-risk medications at follow-up. No significant difference between intervention and control group in proportion of patients rating their care coordination and overall medical care as "excellent" at follow-up. No significant differences in healthcare utilization (i.e. primary care visits, ER visits, hospitalization, hospital days) and healthcare costs during the study between intervention and control group. Incremental healthcare costs were -\$726 per patient per year.

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Counsell et al. [51,52]	cRCT (N = 951)	24	Older adults aged \geq 65 years with an income less than 200% of the federal poverty level.	Primary care by 6 primary care practices in the USA	Geriatric Resources for Assessment and Care of Elders (GRACE) CIS: use of electronic medical record to support physician practices, facilitate monitoring of clinical parameters, and coordination of care across multiple geriatric syndromes, providers, and sites of care. CR: community-based services liaison from primary care practice and affiliated health system is member of interdisciplinary team. DS: training of support team in implementing GRACE protocols and working as interdisciplinary team; use of institutionally endorsed clinical practice guidelines. DSD: GRACE support team (including an advanced practice nurse and social worker) that cares for low income seniors in collaboration with the patient's primary care physician and a geriatrics interdisciplinary team led by a geriatrician; comprehensive geriatric assessment by support team at patient's home; development individualized care plan by GRACE interdisciplinary team; support team discusses individualized care plan with patient's primary care physician; implementation of care plan through contacts with patient, family members or caregivers by support team in collaboration with physician and support by GRACE interdisciplinary team; at least 1 follow-up home visit to review care plan; 1 monthly contact; face-to-face contact after ER visit or hospitalization; coordination of care between providers and settings by support team. SMS: encouragement support team for goal setting and self-care; education by support team in problem-solving skills and in using low-health-literacy materials.	Access to all primary and specialty care services available (i.e. outpatient geriatric assessment and multispecialty centre, inpatient acute care for elders unit and consult centre, skilled nursing facility, physician house calls program, psychiatric care).	<i>Professional caregivers</i> Physicians expressed a high level of support for chronic care levels and believed that they were better able to meet the needs of frail older patients. <i>Patients</i> <i>All patients</i> No significant differences in change over time in ADLs, IADLs, days in bed, and 4 aspects of quality of life (physical functioning, role-physical, bodily pain, role-emotional), physical functioning (physical component summary score of SF-36) between intervention and control group. Significant difference in change over time in the 4 other aspects of quality of life (general health, vitality, social functioning, and mental health) and in mental functioning (mental component summary score of SF-36) between intervention and control group, all in favor of intervention group that improved significantly on these aspects. Total healthcare costs during the study did not differ significantly between intervention and control group: 1. total costs for acute care (i.e. ER and hospitalization) did not differ significantly between intervention and control group; 2. total costs for chronic and preventive care (i.e. GRACE, primary and specialty care, procedures, rehabilitation, mental health) were significantly higher in intervention than in control group. Incremental healthcare costs were \$1321 per patient per year. No significant difference between groups at follow-up in proportion of patients rating their overall satisfaction with care as very good or excellent, mortality, and time to death. ER visit rate was significantly lower during the study in intervention than in control group. No significant difference between groups during the study in hospitalization rate, number of hospital days, and readmission within 30 days after the first hospitalization.

Patients at high risk of hospitalization
ER visit rate and hospital admission rate were significantly lower during the study in intervention than in control group. Number of hospital days during the study did not differ significantly between groups.

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Courtney et al. [67]	RCT (N= 128)	6	Older adults aged ≥65 years with acute medical admission to the hospital and at risk for readmission due to multiple co-morbidities, impaired functionality, age ≥75 years, recent multiple readmissions, poor social support or history of depression.	Hospital care (partly provided at home) by 1 tertiary hospital in Australia	Older Hospitalized Patients' Discharge Planning and In-home Follow-up Protocol (OHP-DP), in addition to usual hospital care. CR: assessment by registered nurse (RN) of need for assistance with activities of daily living and community services. DS: evidence-based exercise intervention; written guidelines on discharge management for the patient (health promotion activities, management of treatment regimens and the exercise plan). DSD: comprehensive patient assessment within 72 h of admission by RN and physiotherapist; design of goal-directed individualized care plan in collaboration with patient, health professionals, family and caregivers. Care plan included: 1. Individualized exercise intervention designed by physiotherapist and facilitated by RN and that started in hospital and continued for 24 weeks. 2. Nursing intervention while patient is in hospital including daily visits of patients by RN in hospital; discharge planning by RN; design transitional care plan by RN including functional ability, need for assistance with activities of daily living, post-discharge treatments and follow-up care, social support, chronic disease management plans and information, medication information, community services, and assistance with exercise program; RN and physiotherapist combined their visits regarding exercise program to ensure continuity. 3. Intervention after discharge including home visit of RN within 48 hours after discharge to assess availability of support, transitional concern, provide advice and support, and ensure safe environment to follow exercise program; extra home visits if necessary; weekly telephone monitoring (advice, information, support) by RN for 4 weeks, thereafter monthly for 5 months. SMS: involvement of patient in designing care plan; diary kept by patient (describing steps and distance recorded with a pedometer).	Usual hospital care (routine care, discharge planning, rehabilitation advice, in-home follow up (if necessary) normally provided).	<i>Patients</i> Number of readmissions, emergency GP visits, and emergency allied health service visits during the study were significantly lower in intervention than in control group. % of patients requiring emergency hospital readmissions and emergency GP visits during the study was significantly lower in intervention than in control group. % of patients requiring ER visits did not differ between groups. Significant difference in change over time in physical component score and mental component score, general health subscale, physical function subscale, role physical subscale, and bodily pain subscale scores between intervention and control group. All in favor of the intervention group that significantly improved on these aspects.

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Daly et al. [72] and Douglas et al. [73]	RCT (N= 334)	2	ICU patients with >72 h mechanical ventilation	Hospital care, nursing home care, and rehabilitation care provided by long-term acute care facility, nursing home, and rehabilitation centre, respectively in the USA.	In addition to usual care, Disease Management Program to reduce hospital readmissions CIS: documentation of all contacts of advanced practice nurse (APN) with patient, family, and healthcare providers using data collection forms. DS: access of APN to pulmonologist and geriatrician for guidance and collaboration by phone (once or twice a month), consultation of hospital care team about patients needs by APN. DSD: case management of APN who meets with patient and family prior to discharge and makes a care plan for the patient, this plan was sent to all relevant out-of-hospital healthcare providers; weekly visits of APN to patients in first 4 weeks and biweekly in next 4 weeks and whenever necessary (in total at least 8 visits); coordination of care by APN. SMS: patients and family are informed about the care plan by the APN; preparation of family for return of patients to their homes; provision of emotional support to family.	When patients and family members asked for advice they were referred back to their primary care provider, extended care facility staff or home care agency.	<i>Patients</i> (IADL) at follow-up did not differ significantly between groups. Total healthcare costs after discharge did not differ significantly between groups. Only costs for readmission during the study differed significantly between groups. Cost savings associated with intervention were \$6198 per readmitted patient. Significantly less total hospital days during readmission during the study in intervention than in control group. Relative risk for hospital readmission, % of patients having > 1 hospital readmission, and mean number of days from hospital discharge to readmission during the study did not differ significantly between groups. Change over time in health-related quality of life at follow-up did not differ significantly between groups. Mortality during readmission and survival rates during the study did not differ significantly between groups.
Dorr et al. [53,54]	CCT (N= 3432, of whom 1671 had complex illness including diabetes)	24	Older adults aged ≥65 years with complex illness.	Primary care by 13 primary care clinics in the USA	Care Management Plus, multidisease care management program CIS: specialized information technology tools (e.g. structured protocols, guidelines, patient worksheet, care management tracking database) for care managers to help manage their patients and to track and react to patient-related data by access to care plans, best practices and facilitating communication through messaging system and documenting all contacts with patients, families, and healthcare providers. CR: care manager and care team focus on linking patients and their caregivers to community resources. DS: training of care managers every other month (e.g. care for seniors, specific chronic illness assessment, care standards); yearly physician training to encourage referral for any complex patient (multiple co-morbidities, frailty) and patients with certain illnesses; guidelines and protocols were regularly revised and updated by local experts. DSD: employment of care managers (registered nurses) in primary care clinic who assesses patients for enrollment in care management services using validated instruments: identification and referral of patients to care manager by physician. HS: administrative and clinical management teams support process and quality improvement at all levels of the organization, and these leaders encourage open discussion of key safety and quality concerns; infrastructure for innovations in treatment of chronic disease that revolves around primary care teams and involves multiple stakeholders; quality indicators to monitor and improve quality of care. SMS: self-management support by care managers; care manager and patient develop care plan together.	N.R.	<i>Patients</i> All patients with complex illness (PQ) hospitalizations and mortality during the study did not differ significantly between groups. Significantly more ER visits during the study in intervention than in control group. <i>Patients with complex illness including diabetes</i> No significant difference in ER visits and (PQ) hospitalizations during the study between intervention and control group. Significantly lower mortality during the study in intervention than in control group.

Duke [55]	Pretest-posttest design (N= 107)	36	Frail community-dwelling elderly aged ≥ 65 years.	Primary care by 1 geriatric clinic in the USA	Frail Elderly Community-Based Case Management Project CIS: telemedicine assessment for medically comprised patients; documentation of all relevant data into electronic database which was used to communicate patients' overall status and to keep physician informed. DS: weekly patient care conferences at geriatric clinic (for case managers, geriatricians, geriatric fellows, support staff, pharmacy and medical students); monthly staff education on patients' needs. DSD: collaboration between primary care physician, geriatric clinic, assisted living community staff, nurse and social-work case manager; case management of medical and social conditions, utilization of hospice and end-of-life decision making; adaptation of interventions to patients' needs. HS: ongoing program development and evaluation by a steering committee. SMS: monthly education by case manager on specific care needs/concerns for patients, family caregivers and assisted living staff.	N.A.	<i>Patients</i> (Changes were not tested for significance) There are indications for decline in cognitive functioning and improvement in perception of quality of life over time. 54% reduction in ER visits over time, resulting in 36% reduction in ER costs. 69% reduction in hospital admissions and 64% reduction in hospital length of stay over time, resulting in 60% reduction in hospital costs (i.e. \$580.189).
Elzen et al. [77]	RCT (N = 144)	6	People aged ≥ 59 years, diagnosed with angina pectoris or heart failure, COPD or asthma, or arthritis, or diabetes, and in addition other (minor) diseases.	Community care provided by hospital/psychologist of the university hospital in the Netherlands	Chronic Disease Self-Management Program (CDSMP) DS: 20 h CDSMP-training of session leaders (pair of peer leader or lay leader and health professional); use of standardized leader manual during CDSMP sessions. DSD: session leaders were a trained psychologist (CDSMP Master Trainer) and a second psychologist or peer leader. SMS: 6-session workshop of 2-1/2 h with 10-13 participants with mixed diagnoses; sessions focused on problem solving, appropriate exercise and medication, communication techniques, nutrition, and how to evaluate new treatments; activities to enhance self-efficacy included weekly action planning, modeling of behaviors, group problem solving, and individual decision-making.	Not specified.	<i>Patients</i> Health behavior (i.e. exercise, cognitive symptom management), health-related quality of life, and perceived self-efficacy at follow-up did not differ significantly between groups. Intervention group was enthusiastic and rated the course with an average of 8.5 (range 0-10). Majority of the group enjoyed the course, indicated it as useful, and was satisfied with course materials, preparations, teaching, length of meetings, group size, and meeting rooms. 25% of the patients indicated the course as strenuous.

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Kobb et al. [40]	CCT (N = 1401)	Ongoing, periodic data collection at 6 month intervals. In this study 12 months follow-up.	Veterans with high-cost medical care needs (>\$25,000) and high use (two or more hospital admissions, frequent emergency room visits, and unscheduled walk-in visits, and 10 or more prescriptions) in the year preceding enrollment.	Home care provided by Veterans Health Administration in the USA	Rural Home Care Project (RHCP) (see Chumbler et al. [79])	N.R.	<i>Patients</i> (Changes were not tested for significance) Healthcare utilization (i.e. hospital admissions, bed days of care, nursing home admissions, nursing home bed days of care, ER visits, clinic visits, pharmacy visits) at follow-up was lower for intervention group and higher for control group. Health utilization decreased in the intervention groups whereas it increased in the control group. Overall, both groups improved in 3 aspects of health-related quality of life over time (i.e. physical health, mental health, and social functioning) and remained stable in the other aspects (physical role, bodily pain, general health, vitality, emotional role). Intervention group using Health Buddy device improved from being not compliant with immunization usage (hypertensive medication, influenza and pneumococcal vaccines) to 90-92% compliant. Medication compliance by patients in the intervention group increased from 68% to 93%. Intervention group reported high levels of satisfaction with project team members and technology and found the technology easy to use and helpful in managing their chronic conditions. <i>Professional caregivers</i> Providers reported high satisfaction reflected by the majority of providers valuing the communication between their selves and care coordinator timely/appropriate; finding RHCP of benefit to their patients; and willingness to refer patients to RHCP.

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Krause et al. [64]	Pretest-posttest design (N=39)	12	Patients with multiple chronic conditions.	Hospital care provided by different hospitals in the USA.	Integrated multidisciplinary advocacy program DSD: multidisciplinary team of health advocates (not specified) to review physical and psychological medical records and performing an extensive multidisciplinary, whole-person intake assessment of patient. SMS: advocate team collaborates with patient to design integrated plan with goals for improvement in self-efficacy, education and experience in appropriate use of the health care system as well as whole-person, family, financial, and social well-being.	N.A.	Patients Rating of effectiveness of healthcare services under the program in helping them to deal with their conditions and satisfaction with healthcare services was significantly higher at follow-up than at baseline. Patients reported to exercise significantly more and to eat significantly healthier at follow-up than at baseline. Healthcare costs were significantly lower than projected costs (using HCUP-3 data). Health-related quality of life was significantly higher at follow-up than at baseline. Participants perceived their physical well-being significantly higher at follow-up than at baseline. Life satisfaction was significantly higher at follow-up than at baseline. Locus of control at follow-up did not differ significantly from locus of control at baseline. Self-efficacy regarding patient's ability to manage their healthcare needs was significantly higher at follow-up than at baseline.
Leveille et al. [56]	RCT (N=201)	12	Frail older people aged ≥70 years with ≥1 chronic illness	Primary/ community care by a senior center in the USA.	Health Enhancement Project (HEP) CR: partnership of community senior center with primary care; referral of patients to senior center or community programs in case of smoking and excessive alcohol use. DSD: collection of information at GP by Geriatric Nurse Practitioner (GNP) on current health problems of patients and GP's goals; reports were sent to GPs to inform them about participation of patient in program; sessions with patients with GNP at senior centre; monitoring of progress towards health goals by follow-up visits and phone contact; changes in medication were discussed with GP; referral to specialized programs of caregivers if necessary (smoking, alcohol abuse, depression). SMS: design of targeted health management plan by GNP and patient addressing risk factors for disability and self-management issues; individual counseling by GNP in chronic illness self-management; encouragement of patients to attend physical activities at senior center or to perform activities at home and to attend chronic illness self-management course (7 week, 2 h) conducted by trained lay leaders (combining peer support with health promotion information and disease management concepts) using a self-management workbook; provision of nutrition tip sheets developed in consultation with registered dietitians.	Patients were given a tour of the senior center and a list of scheduled activities. They did not meet with GNP but had access to all senior centre activities that were available to the intervention group.	Patients Change in ADL significantly differed between groups, in favor of intervention group. Attitude and behavior related to physical activity at follow-up were significantly better in intervention than in control group. Alcohol use, smoking status, and nutritional risk at follow-up did not differ significantly between groups. Change in depressive symptoms and health-related quality of life over time did not differ significantly between groups. Significantly fewer bed disability days at follow-up in intervention than in control group. Restricted activity days did not differ significantly between groups. Change in total number of hospital days differed significantly between groups, in favor of intervention group. Change in number of hospitalized patients, ER visits, and outpatient visits over time did not differ significantly between groups. Senior centre participation was significantly higher at follow-up in intervention than in control group. Use of psychoactive drugs at follow-up was significantly lower in intervention group than in control group. Change in physical performance over time did not differ significantly between groups. Physical performance measured with PASE at follow-up was significantly higher in intervention than in control group.

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Liddy et al. [41]	Post-test only study (N=22; purposeful sample of a larger RCT)	Time of measurement was variable and depended on period telehome care units were used (9-339 days)	People aged ≥50 years at risk for functional decline or physical deterioration.	Primary care by 1 primary care practice (i.e. family health network) in Canada	Telehomecare CIS: tele-homecare unit installed at patient's home; use of remote home-based monitoring equipment linked to offices of primary care providers. DSD: individualized care plan collaboratively developed by primary care physician, nurse practitioner, and pharmacist. SMS: training to enter clinical data on vital signs and health information into the system, either manually or through supplied peripherals.	N.A.	Patients Patients found the technology user-friendly and useful. Informal caregivers Informal caregivers found the technology user-friendly and useful. Professional caregivers Healthcare providers were satisfied with the technology and found equipment useful; they thought it might reduce number of office visits and track long-term trends.
Littleford and Kraik [57]	Pretest-posttest design (pilot study) (N=220)	Variable, depending on admission to ICCOP in the 24 month pilot period.	Older people aged ≥65 years or Aboriginals aged ≥45 years with multiple complex health problems and at risk of or with a history of frequent unplanned hospital admissions or ER visits.	Integrated community care by a partnership between a community nursing organization, GP practice, and hospital in Australia	Integrated Community Care for Older People (ICCOP) CIS: assessments and care plans are hosted on secure ICCOP website in individualized client e-health records which are accessible for GP, geriatrician, ED medical staff, and ICCOP nurse. CR: referral to appropriate services of community service system to meet complex needs of patients. DS: collaboration and sharing of knowledge between involved disciplines to manage patient. DSD: referral of patients to ICCOP by geriatrician or GP; transfer of referral to ICCOP nurse who contacts patient for geriatric assessment; design care plan (including health goals, actions to be taken) by ICCOP nurse based on geriatric assessment; regular update of care plan based on events and contacts; admission and care plan discussed with patient, family, GP, practice nurse and geriatrician; cooperation between health and care professionals, patients and services; coordination of provision of care and funding for care by ICCOP nurse; involvement of ICCOP nurse in discharge planning. SMS: cooperation of ICCOP nurse with patients to establish desired health goals.	N.A.	Patients ER visits reduced with 51% during the study compared with the number of visits before enrollment. Hospital length of stay reduced with 37% during the study compared with the total number of hospital days before enrollment.

Markle-Reid et al. [58]	RCT (N=288)	6	Frail older people aged ≥ 75 years eligible for home care services.	Home care by home care organization in Canada	In addition to usual home care, proactive nursing health promotion intervention CR: referral to and coordination of community services. DSD: health assessment to support personal resources; identifying and managing risk factors for functional decline; regular home visits or telephone contacts by registered nurse from a community-nursing agency; providing caregiver support. SMS: health education by registered nurse about management of illness and healthy lifestyles using empowerment strategies.	Usual home care services consisting of case management, personal care, home support (home making), nursing, occupational therapy, physiotherapy, social work, and speech language therapy through community-based agencies.	<p>Patients</p> <ul style="list-style-type: none"> Change over time in coping styles did not differ significantly between groups. Change over time in depressive symptoms differed significantly between groups, in favor of the intervention group that had a significantly greater reduction in depressive symptoms. No significant difference between groups during the study in mean costs of all types of health and social services, and the total annual per person direct costs of health services. Significantly lower per person cost of prescription medications in intervention than in control group. Change over time in physical function, role functioning related to physical health, bodily pain, general health perception, vitality, social functioning, and physical health component summary score did not differ significantly between groups. Change over time in role functioning related to emotional health, mental health, and mental health component summary score differed significantly between groups, in favor of the intervention group that significantly improved on these aspects. Change over time in perceived social support differed significantly between groups, in favor of the intervention group that experienced a significant increase of social support.
Marsteller et al. [59]	cRCT (N=49)	12	Primary care physicians providing care to multimorbid people aged ≥ 65 years and at high risk for incurring high healthcare costs in the coming year.	Primary care by 8 primary care practices in the USA	Guided Care (see Boulton et al. [45])	Not specified	<p>Professional caregivers</p> <ul style="list-style-type: none"> Knowledge of the clinical characteristics of patients and satisfaction with patient/family communication at follow-up were significantly higher in physicians providing guided care than in physicians providing usual care. No significant differences between physicians from both groups at follow-up with regard to satisfaction with care management, time spent on chronic care, knowledge of patients' personal circumstances, and care coordination.

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Mitton et al. [60]	Pretest-posttest design (N=37)	12	Older patients with high healthcare needs and chronic or complex medical problems.	Primary care by collaborative partnership between home care organization and primary care practice in Canada.	<p>Nurse Physician Collaborative Partnership</p> <p>CIS: electronic patient health record system in which nurses could access patients' records and communicate with physicians by e-mail. CR: linkage to community supports (no further details available). DS: shared care guidelines; professional courses for project nurses with knowledge and skill gaps; consultation with partners and other healthcare providers (e.g. pharmacist); discussion between nurse and physician at monthly care planning meeting. DSD: collaborative partnership between home care nurses and family physicians, services included referral and admissions, development, and modification of shared care plan for each patient; comprehensive biopsychological assessment; active patient management; standard and advanced nursing interventions. SMS: health education and self management.</p>	NA	<p>Patients</p> <ul style="list-style-type: none"> ADL, cognitive functioning, and health-related quality of life at follow-up did not differ significantly from ADL, cognitive functioning, and health-related quality of life at baseline. Total healthcare costs significantly decreased during the study, mainly due to significantly less inpatient costs than in the year preceding the study. Other healthcare costs did not change significantly during the study. However, when program costs were included, total healthcare costs did not differ significantly with the year preceding the study, although they were \$2463 lower per patient. Healthcare utilization decreased during the study: 25% reduction in hospital admissions, 50% reduction in days spent in hospital, 32% reduction in ER visits, 28% reduction in visits for diagnostic tests, 15% reduction in ambulatory care visits. Patients reported periods of improved health and felt well cared for. They particularly appreciated nurse-physician partnership, the holistic approach, the early intervention, technological capabilities, and connections to other healthcare providers. <p>Informal caregivers (N = not reported)</p> <ul style="list-style-type: none"> Caregivers appreciated the improved access and quality of services. They reported decreased anxiety and improved ability to cope (not tested for statistical significance). <p>Professional caregivers (N = not reported)</p> <ul style="list-style-type: none"> (Changes not tested for significance) Small changes in job satisfaction of physicians and nurses at follow-up compared to baseline. Partnership improved accessibility and availability, enabled continuity of care, and enabled effective case management. Pharmaceutical knowledge and interpretation of laboratory tests were the 2 major areas of additional learning for nurses.

Naylor et al. [74]	RCT (N=239)	12	Patients aged 65 or older and hospitalized with heart failure.	Hospital care by 6 hospitals in the USA	<p>Transitional care intervention</p> <p>DS: standardized orientation and training program guided by a multidisciplinary team of heart failure experts to prepare the advanced practice nurse (APN) to address the unique needs of older adults and their caregivers throughout an acute episode of heart failure; implementation of an evidence-based protocol designed for patients with an acute episode of heart failure complicated by multiple co-morbid conditions.</p> <p>DSD: 3-month APN-directed discharge planning and home follow-up protocol; use of care management strategies including identification of patient's and caregiver's goals, individualized care plans designed and implemented by APN in collaboration with patient's physicians; use of expert nurses to deliver and manage clinical services to high risk patients; continuity of care and care coordination across settings; initial APN visit within 24 hours of index hospitalization; daily visits during hospitalization and at least 8 visits at home after discharge (first weekly then biweekly during second and third month) for monitoring and in home assessments; 24/7 availability of APN by phone.</p> <p>SMS: APN performs educational and behavioral strategies to address patients' and caregivers' learning needs</p>	<p>Routine care provided by the admitting hospital, including site-specific heart failure patient management and discharge planning critical paths, and if referred, standard home care agency care.</p> <p>The discharge planning was similar in all hospitals, also home care was similar. Home care included use of liaison nurses, availability of skilled home care services, and nurse 24 a day hours on call.</p>	<p>Patients</p> <p>ADL, health-related quality of life, and mortality at follow-up did not differ significantly between groups.</p> <p>Healthcare costs during the study were significantly lower in intervention than in control group. Incremental healthcare costs were ~\$708 per patient per year.</p> <p>Number of rehospitalizations during the study was significantly lower in intervention than in control group. Time to first readmission was significantly longer in intervention than in control group. Number of patients requiring readmission and number of hospital days during the study did not differ significantly between groups.</p> <p>Patient satisfaction at 6 weeks follow-up was significantly higher in intervention group than control group.</p>
Procter and Single [42]	Pretest-posttest design (N= 25)	4	Older people aged >65 years, diagnosed with heart failure or COPD and early stage dementia (combinations with other chronic conditions were allowed), living at home, and experiencing repeated hospital admissions.	Primary care in the UK, setting unknown.	<p>Home Telehealth care</p> <p>CIS: installation tele-homecare unit at patient's home for biometric monitoring; observations required by clinician were discussed with patient, tele-homecare unit was programmed to prompt patient to undertake these observations on daily basis; results were downloaded to a central web-based server which was accessed daily by a nurse; tele-monitoring equipment was programmed to ask patients a series of questions about their health; equipment could be programmed to remind patients to take their medications and to attend appointments; system could be adapted for new observations.</p> <p>CR: liaison with other providers.</p> <p>DSD: project nurse was appointed and was responsible for assessing patient, developing care plan, installing tele-monitoring equipment, and daily monitoring; in case daily monitoring identified problems, nurse contacted patient (telephone or home visit) or arranged GP visit; nurse was first contact for any technical difficulties experienced by patients; nurse negotiated with patient and healthcare providers and was a liaison for other healthcare providers.</p> <p>SMS: patients enter and upload measurement results (of vital signs) daily; reminders on medication and appointments (hospital and GP).</p>	NA.	<p>Patients</p> <p>(Changes were not tested for significance)</p> <p>Patients reported increased confidence in managing diseases at follow-up.</p> <p>Number of hospitalizations decreased with 38% during the study.</p> <p>Informal caregivers</p> <p>Informal caregivers reported increased confidence in managing diseases at follow-up.</p> <p>Professional caregivers</p> <p>In 14 out of 25 patients early detection and treatment of problems occurred during the study.</p>

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Rose et al. [78]	Pretest-posttest design (N= 175)	6	Low income older urban African American adults with ≥1 chronic condition.	Community care provided by community sites (i.e. senior citizen centers, senior housing for low income older people, churches) in the USA.	<p>Chronic Disease Self-Management Program (CDSMP) (see Elzen et al. [77])</p> <p>DSD: in addition to session leaders reported by Elzen et al. [77] co-leaders were lay African American older adults, who were part of the community.</p> <p>SMS: workshops consisted of 10-20 participants instead of 10-13 participants as reported by Elzen et al. [77].</p>	N.A.	<p>Patients</p> <p>Health behavior regarding stretching or strengthening exercise and communication with GP was significantly improved at follow-up. Health behavior regarding cognitive symptom management and aerobic exercise was not changed significantly at follow-up.</p> <p>Health-related quality of life, impact of disease on role and social activities, perceived self-efficacy, and role function were not changed significantly at follow-up, with the exception of energy that was significantly improved.</p> <p>Healthcare utilization (i.e. GP visits, ER visits, hospital stays, nights in hospital) was not changed significantly at follow-up.</p>
Rubenstein et al. [61]	RCT (N= 792)	36	Community-dwelling veterans aged ≥65 years with at least 1 clinic visit in the last 18 months.	Primary care provided by Department of Veterans affairs ambulatory care centre in the USA.	<p>Managed care plus screening, case finding, and referral system for older veterans in primary care</p> <p>DS: supervision of case manager by study geriatricians; structured format to validate and clarify positive findings from structured geriatric telephone assessment of patient.</p> <p>DSD: structured geriatric telephone assessment of specific risks and unmet needs by physician assistant case manager; specific referrals and recommendations by case manager to further assess, treat, and manage unmet needs; coordinated outpatient follow up by case manager; referral of patients to either geriatric assessment clinic, home-based primary care program or primary care provider or other specific services; provision of overview of recommendations, referrals, and scheduled appointments to patient by case manager; on-going telephone case management (every 3 months) to encourage patients to adhere to referrals and recommendations and to monitor changes in health.</p> <p>SMS: health promotion recommendations and health education by case manager to patient.</p>	Managed care without screening, case finding and referral system.	<p>Patients</p> <p>Change over time in (1)ADL, depressive symptoms, fall incidence, health-related quality of life, and urinary incontinence did not differ significantly between groups.</p> <p>Healthcare utilization (i.e. number of hospital days, number of patients admitted to hospital) during the study did not differ significantly between groups.</p>

Saltvedt et al. [68,69]	RCT (N= 254)	12	Acutely sick, frail older patients aged ≥ 75 years who were acutely admitted hospital.	Hospital care by 1 hospital in Norway.	Geriatric Evaluation Management Unit (GEMU) DS: Meetings of all disciplines (twice a week) to report assessments, discuss problems, set goals, and plan discharge. Primary health care nurses were telephoned to discuss arrangements of discharge, when considered appropriate by the staff DSD: interdisciplinary approach with close collaboration between all disciplines; design individual rehabilitation plans for each patient.	Usual treatment of Department of Internal Medicine	<p><i>Patients</i></p> <p>(JADL, general well-being, depression, and cognitive functioning at follow-up did not differ significantly between groups. % of patients deceased at follow-up did not differ significantly between groups. Heart disease was the major cause of death in both groups. During the study infections were more frequently the cause of death in the intervention than in the control group.</p>
Schmader et al. [70]	RCT (N= 864)	Inpatient period: variable Outpatient period: 12 months minus inpatient period.	Hospitalized frail veterans aged ≥ 65 year admitted to a medical or surgical ward for ≥ 3 days.	Hospital care by 11 Veterans Affairs medical centers in the USA.	Geriatric Evaluation and Management (GEM) In addition to GEM described by Burns et al. (1995); DS: evaluation and management by team members according to published guidelines and Veterans Affairs' standards for patients. DSD: team consisting of geriatrician, social worker, and nurse; implementation of evaluation and management protocols for GEM patients by team; regular assessments and recommendations regarding medications by pharmacists.	Usual inpatient care: customary medical or surgical treatment by physicians (or others under their direction). Usual outpatient care: customary care delivered by ambulatory care physicians (or others under their direction).	<p><i>Patients</i></p> <p><i>Inpatient period</i></p> <p>Total number of detected adverse drug reactions during the study was significantly higher in intervention than in control group. Change in number of unnecessary drugs, in medication appropriateness, in number of inappropriate drugs, and in number of conditions with omitted drugs during the study was significantly larger in intervention than in control group, all in favor of the intervention group.</p> <p><i>Outpatient period</i></p> <p>Total number of detected adverse drug reactions during the study did not differ significantly between groups. Number of detected serious adverse drug reactions was significantly higher in intervention than in control group. Change in number of unnecessary drugs, medication appropriateness, and number of inappropriate drugs during the study did not differ significantly between groups. Change in number of conditions with omitted drugs during the study was significantly smaller in intervention than in control group, in favor of the intervention group.</p>

Table 1 (Continued)

Author (year)	Study design (N) ^a	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Sorrento et al. [62]	Pretest-posttest design (N= 273)	N.R.	Community-dwelling older people aged ≥ 75 years with ≥ 2 chronic illnesses and with ≥ 1 of the following problems: memory deficits, history of falls, incontinence, depression, anxiety, and/or malnutrition.	Primary care provided by partnership of physicians and hospitals in the USA.	Geriatric Assessment Service (GAS) DS: weekly team meeting discussing all enrolled patients and determining the disciplines initiating the evaluation; use of standardized instrument to evaluate aspects of patients' functioning, impairments and social support. DSD: multidimensional evaluations of patients by interdisciplinary team (consultant pharmacist, social worker, registered nurse); home evaluations by nurse and/or social worker (required assessments varied according to needs of patients); involvement of consultant pharmacist in screening patients identified as at-risk by primary care provider and in evaluating appropriateness of medication regimens; results of all assessments, goals, recommendations and plans were written in a summary letter that was sent to GP and who decided which actions should be undertaken. SMS: family/caregiver education and recommendations to improve medication management by pharmacist.	N.A.	<p><i>Patients</i></p> <p>(Changes were not tested for significance). On average 62% of patients reported an improvement in medication management at follow-up. On average 90% of the patients was satisfied with the program. Informal caregivers (n= 13) reported on average a 28% improvement in caregiver burden at follow-up.</p>
Taylor et al. [76]	RCT (N= 169)	12	Patients with longstanding diabetes with one or more major medical co-morbid conditions (hypertension, dyslipidemia or CVD) and HbA1c $> 10\%$.	Primary care provided by managed care organization in the USA.	Nurse Care Management System DS: treatment algorithms based on national guidelines used by nurse care-managers use: education for nurse-care managers on diabetes, cholesterol, hypertension, and depression. DSD: initial individual meeting with a registered nurse to assess patients health status and needs; telephone follow-up calls by program nurse manager; primary care physician was called if a new medication was indicated or to report any unusual findings. SMS: development initial self-management plan; group classes once a week for 4 weeks, with focus on group discussion, participation, and problem-solving; about 8 telephone follow-up calls to review patients' goals and medical outcomes.	Usual medical care, patients were instructed and encouraged to remain under care of their physician, got a folder with information on diabetes and a Medical Alert pamphlet, and were encouraged to attend general diabetes education.	<p><i>Patients</i></p> <p>Depression improved significantly over time in both groups. Change over time in depression and health-related quality of life did not differ significantly between groups. Healthcare utilization (i.e. GP visits, ER visits, hospitalizations) during the study did not change significantly within both groups and did not differ significantly between groups. Changes over time in HbA1c, total, and LDL cholesterol differed significantly between groups, in favor of intervention group that improved significantly on these outcomes whereas control group did not change significantly over time. Changes in fasting glucose, systolic and diastolic blood pressure, and BMI were not significant within both groups and did not differ significantly between groups. Significantly larger % of patients in the intervention group than in the control group met the goals for HbA1c (i.e. HbA1c $< 7.5\%$) at follow-up. % of patients meeting the other outcome goals did not differ between groups. 90% of patients indicated at follow-up that they found the program moderately to extremely helpful. 92% of patients indicated at follow-up that the program was moderately to extremely helpful in preparing them to self-manage their conditions. Patients reported high levels of confidence to engage in the behaviors necessary to manage their diabetes. Confidence increased in both groups over time.</p>

Author (year)	Study design (N ^a)	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Tibaldi et al. [71]	RCT (N = 109)		Frail older patients with dementia requiring admission to a hospital emergency department for acute illness.	Hospital care (provided at home) by 1 hospital in Italy	Geriatric Home Hospitalization Service (GHHS) DSD: GHHS team (5 geriatricians, 14 nurses, 4 physiotherapists, 1 dietician, 1 social worker, 1 counselor) providing physician and nursing care, medicines, and appropriate diagnostic and therapeutic interventions at home; service operates 12 h a day 7 days a week; GHHS doctors and nurses are available for patients at all times. SMS: caregivers are informed about the emergency plan and encouraged to telephone if problems or questions arise.	Admission to general medical ward.	<i>Professional caregivers (N = 13)</i> 69% of caregivers indicated that they strongly recommended adoption of the program by their healthcare system, that they felt that the program decreased time spent with patients. 31% indicated that they felt that the program increased the time spent with patients. <i>Patients</i> Significantly lower % of patients with behavioral disturbances (i.e. sleeping disorders, agitation, feeding disorders) and using antipsychotic drugs at discharge in intervention than in control group. No significant difference in mortality during the study between groups. <i>Informal caregivers</i> Change in caregiver stress over time was significantly larger in intervention than in control group, in favor of the intervention group where caregiver stress reduced significantly.
Wright et al. [11]	Post-test only study (without control) (pilot) (N = 118)	Time of measurement was 12 months after start of AD-LIFE	Low-income older patients with chronic conditions and functional impairment at high risk for re-hospitalization or nursing home placement.	Primary care by non-profit healthcare delivery network in the USA.	After Discharge Care Management of Low-Income Frail Elderly (AD-LIFE) (integrated medical and social care) DS: use of evidence-based protocols for designing care plan; education of primary care physicians regarding care management process. DSD: advanced practice nurse assesses eligible patients for program at admission and assist discharge planning; assessment findings are shared with hospital-based interdisciplinary team that includes patient, geriatrician, registered nurse (RN) care manager, pharmacist, social worker, and possible other healthcare providers; team generates care plan; RN care manager implements care plan after discharge in collaboration with patient's primary care physician and provides ongoing follow-up evaluation; each primary care practice gets assigned own RN care manager; reimbursement for primary care physicians to review care plans and receive updates; follow-up by RN care manager to check whether patient implements recommendations.	N.A.	<i>Patients</i> Number of hospital admissions per 1000 patients decreased resulting in decreased healthcare costs of \$12260 per patient per year during the study (not tested for significance). About 70% of patients indicated at follow-up that the program had improved their health, had made it easier to get healthcare services, had them provided with a better understanding of their disease, and had not experienced a subjective decline in health during the year. 93% of patients rated their experience as "good" or "excellent" and 92% of patients would recommend program to their friends. <i>Professional caregivers</i> Physicians indicated to be highly satisfied at follow-up.

Table 1 (Continued)

Author (year)	Study design (N ^a)	Length of follow-up (months) ^b	Target population	Setting	Contents of comprehensive care program ^c	Usual care ^d	Outcomes ^e
Zhang et al. [75]	CCT (N = 65132)	24	Medicaid patients having one of five of the following diseases: diabetes, hypertension/congestive heart failure, depression, gastro-esophageal reflux disease/peptic ulcer disease and Asthma/COPD and/or co-morbidities.	Primary and/or pharmaceutical care by primary care practices and/or pharmacies in the USA	Disease State Management (DSM) program I ₁ : physicians intervened I ₂ : both physicians and pharmacists intervened CIS: Mailing with claims-data based routine feedback sheet and clinical summary with latest results on outcome measures. DS: Mailing of educational materials on the five diseases and their co-morbidities on quarterly basis for 3 years to participating physicians and pharmacists. SMS: physicians and pharmacists were asked to consult with their patients and/or patient representatives about their life styles, treatment, and drug use.	No interventions	<i>Patients</i> <i>Patients with co-morbidity</i> Change in ER visits and hospitalizations over time differed significantly between intervention groups and control group, in favor of the control group. Change in GP visits did not differ significantly between intervention group 1 and control group and differed significantly between intervention group 2 and control group, in favor of control group and between intervention group 1 and 2, in favor of intervention group 1. <i>All patients</i> Overall, health-related quality of life deteriorated over time. Health-related quality of life reduced significantly slower over time in the intervention groups than in the control group for 9 of 11 subscales (mental, social, general, and perceived health, self-esteem, anxiety, depression, anxiety/depression, and disability). Average cost savings per hospitalization for intervention group were \$50. It was estimated that the program would save approximately \$1.8 million/year during the study, and would achieve a \$2.0 return for each dollar invested.

^a CCT = controlled clinical trial; cRCT = cluster-randomized controlled trial; RCT = randomized controlled trial; N = the number of patients/caregivers allocated at study entry.

^b N.A. = not applicable.

^c CIS = clinical information system; CR = community resources; DS = decision support; DSD = delivery system design; HS = health system; SMS = self management support.

^d N.A. = not applicable; N.R. = not reported.

^e ADL = activities of daily living; ER = emergency room; FIM = Functional Independence Measure; GP = general practitioner; HbA1c = glycated hemoglobin; HCUP = Healthcare Cost and Utilization Project; IADL = instrumental activities of daily living; LDL = low-density lipoprotein; MMSE = Mini Mental State Examination; PASE = Physical Activity Scale for the Elderly; PQJ hospitalization = hospitalization for one of the prevention quality indicators; SF-36 = Medical Outcomes 36-item short-form.

Table 2
Results of methodological quality assessment of included studies.

Study	Randomization ^a	Similar at baseline ^b	Compliance ^c	Drop-out rate ^d	ITT-analysis ^e	Adjustments for confounding variables in analysis ^f	Total score
Anonymous [63]	N.A.	N.A.	?	N.A.	N.A.	N.A.	0
Béland et al. [43]	+	+	?	+	+	+	5
Boult et al., Boyd et al., Leff et al., and Wolff et al. [44-47]	+	-	?	+	+	+	4
Boyd et al. and Sylvia et al. [48,49]	N.A.	-	?	+	+	?	2
Brand et al. [65]	N.A.	-	?	+	N.A.	+	2
Burns et al. [66]	+	+	?	?	-	N.A.	2
Chumbler et al. [79]	N.A.	-	?	+	N.A.	+	2
Coleman et al. [50]	?	+	?	+	+	+	4
Counsell et al. [51,52]	+	+	?	+	+	N.A.	4
Courtney et al. [67]	+	+	?	+	+	N.A.	4
Daly et al. and Douglas et al. [72,73]	+	+	?	?	-	N.A.	2
Dorr et al. [53,54]	N.A.	+	?	+	N.A.	N.A.	2
Duke et al. [55]	N.A.	N.A.	?	+	N.A.	N.A.	1
Elzen et al. [77]	+	+	?	+	-	N.A.	3
Kobb et al. [40]	N.A.	?	+	+	N.A.	?	2
Krause et al. [64]	N.A.	N.A.	?	+	N.A.	N.A.	1
Leveille et al. [56]	+	-	?	+	+	+	4
Liddy et al. [41]	N.A.	N.A.	+	N.A.	N.A.	N.A.	1
Littleford and Kralik [57]	N.A.	N.A.	?	+	N.A.	N.A.	1
Markle - Reid et al. [58]	+	+	?	+	+	N.A.	4
Marsteller et al. [59]	?	+	?	+	-	?	2
Mitton et al. [60]	N.A.	N.A.	?	+	N.A.	N.A.	1
Naylor et al. [74]	+	+	?	+	+	N.A.	4
Procter and Single [42]	N.A.	N.A.	-	?	N.A.	N.A.	0
Rose et al. [78]	N.A.	N.A.	?	-	N.A.	N.A.	0
Rubenstein et al. [61]	?	+	?	+	+	?	3
Saltvedt et al. [68,69]	+	+	?	+	-	N.A.	3
Schmader et al. [70]	+	+	?	?	-	N.A.	2
Sorrento et al. [62]	N.A.	N.A.	?	?	N.A.	N.A.	0
Taylor et al. [76]	?	+	?	+	-	N.A.	2
Tibaldi et al. [71]	?	?	?	?	+	?	1
Wright et al. [11]	N.A.	N.A.	?	N.A.	N.A.	N.A.	0
Zhang et al. [75]	N.A.	?	?	?	N.A.	N.A.	0

N.A. = not applicable; +- criterion fulfilled; -- criterion not fulfilled; ? = lack of information.

^a Was the method of randomization adequate?

^b Were the groups similar at baseline regarding the most important prognostic indicators?

^c Was the compliance of patients acceptable in all groups?

^d Was the drop-out rate described and acceptable?

^e Did the analysis include an intention-to-treat analysis.

^f Are adjustments made for confounding variables and/or differences in prognostic indicators at baseline?

Table 3a
Clinical patient outcomes (mean (SD)) of studies evaluating impact of comprehensive care programs for multimorbid patients.*

Study	Study design (N) ^a	Measuring instrument ^b	Comprehensive care group ^c		Usual care group		p
			Baseline	Follow-up	Baseline	Follow-up	
<i>Cognitive functioning</i>							
Burns et al. [66]	RCT (N= 130)	MMSE	24.6 (3.6)	25.8 (3.2)	24.5 (3.1)	24.7 (3.8)	>0.05, for group difference <0.01, for time change >0.05, for interaction effect
Chumbler et al. [79]	Case control design in which subjects receiving comprehensive care were compared with subjects from another longitudinal study (N = 226)	MMSE FIM cognitive subscale	20.8 (6.8) 29.2 (5.2)	25.8 (4.7) 31.8 (5.3)	26.2 (6.4) 31.3 (6.8)	28.2 (6.4) 31.0 (6.7)	0.59, for group difference <0.0001, idem
Duke et al. [55]	Pretest-posttest design (N = 107)	MMSE	N.R.	N.R.	-	-	N.R.
Mitton et al. [60]	Pretest-posttest design (N = 37)	MMSE	N.R.	N.R.	-	-	0.32, for time change
Saltvedt et al. [68,69]	RCT (N = 254)	MMSE	~25.0 (N.R.)	~25.0 (N.R.)	~25.1 (N.R.)	~24.9 (N.R.)	>0.05, for group difference
<i>Depressive symptoms</i>							
Burns et al. [66]	RCT (N = 130)	CES-D	10.9 (11.0)	3.9 (5.2)	11.7 (10.6)	7.6 (7.1)	<0.01, for group difference <0.001, for time change <0.05, for interaction effect
Coleman et al. [50]	RCT (N = 169)	CES-D	11.4 (N.R.)	14.8 (N.R.)	15.9 (N.R.)	12.4 (N.R.)	0.19, for group difference
Leveille et al. [56]	RCT (N = 201)	CES-D	10.1 (8.0)	N.R.	8.7 (7.3)	N.R.	0.526, for group difference
Markle - Reid et al. [58]	RCT (N = 288)	CES-D	15.8 (10.0)	11.9 (10.2)	12.9 (8.5)	11.8 (10.7)	0.022, for group difference
Rubenstein et al. [61]	RCT (N = 792)	GDS-15	5.0 (3.6)	3.9 (3.2)	5.2 (3.7)	3.4 (3.4)	>0.05, for group difference
Saltvedt et al. [68,69]	RCT (N = 254)	MADRS	N.R.	N.R.	N.R.	N.R.	>0.05, for group difference
Taylor et al. [76]	RCT (N = 169)	BDI	N.R.	N.R.	N.R.	N.R.	N.R.
<i>Functional status</i>							
Burns et al. [66]	RCT (N = 130)	Katz ADL	0.3 (0.8)	0.2 (0.7)	0.5 (1.1)	0.4 (1.0)	>0.05, for group difference <0.01, for time change >0.05, for interaction effect
		IADL	11.6 (5.4)	11.9 (6.2)	10.9 (4.1)	12.7 (6.1)	>0.05, for group difference <0.01, for change over time >0.05 for interaction effect
Chumbler et al. [79]	Case control design in which subjects receiving comprehensive care were compared with subjects from another longitudinal study (N = 226)	FIM motor subscale IADL	85.3 (21.9) 9.0 (4.3)	99.2 (15.2) 11.4 (3.1)	73.9 (14.2) 8.6 (4.1)	73.3 (14.5) 8.3 (4.2)	<0.0001, for group difference <0.0001, idem

Table 3a (Continued)

Study	Study design (N) ^a	Measuring instrument ^b	Comprehensive care group ^c		Usual care group		p
			Baseline	Follow-up	Baseline	Follow-up	
Counsell et al. [51,52]	cRCT (N = 951)	AHEAD (ADL items) AHEAD (IADL items)	1.6 (3.1) 2.7 (4.2)	N.R. N.R.	1.3 (2.6) 2.5 (3.9)	N.R. N.R.	0.37, for group difference 0.77, idem
Douglas et al. [73]	RCT (N = 334)	OASIS	N.R.	24.5 (11.6)	N.R.	22.5 (13.5)	0.33, for group difference
Leveille et al. [56]	RCT (N = 201)	HAQ	0.24 (0.32)	N.R.	0.23 (0.34)	N.R.	0.014, for group difference
Mitton et al. [60]	Pretest-posttest design (N = 37)	Barthel index	N.R.	N.R.	-	-	N.R.
Naylor et al. [74]	RCT (N = 239)	ESDS	3.3 (1.1)	3.1 (1.5)	3.3 (1.1)	2.9 (1.6)	>0.10, for group difference
Rubenstein et al. [61]	RCT (N = 792)	FSQ (ADL items) FSQ (IADL items)	84.1 (19.6) 53.9 (26.3)	82.4 (22.1) 56.5 (32.9)	82.8 (20.4) 53.4 (28.6)	85.2 (20.6) 58.2 (31.7)	>0.05, for group difference idem
Saltvedt et al. [68,69]	RCT (N = 254)	Barthel index IADL	~15.5 (N.R.) ~4.0 (N.R.)	~15.0 (N.R.) ~4.2 (N.R.)	~16.0 (N.R.) ~4.2 (N.R.)	~15.0 (N.R.) 4.1 (N.R.)	>0.05, for group difference >0.05, idem
<i>Health behavior</i>							
Eizen et al. [77]	RCT (N = 144)	Exercise (Lorig) Cognitive symptom management (Lorig) Communication with physician (Lorig)	N.R. N.R. N.R.	N.R. N.R. N.R.	N.R. N.R. N.R.	N.R. N.R. N.R.	0.47, for group difference 0.14, idem 0.48, idem
Kobb et al. [40]	CCT (N = 1401)	Immunization compliance Medication compliance	N.R. N.R.	N.R. N.R.	N.R. N.R.	N.R. N.R.	Not tested for significance Not tested for significance
Krause et al. [64]	Pretest-posttest design (N = 39)	PPCQ (exercise) PPCQ (healthy eating)	2.49 (1.49) 3.69 (1.15)	3.64 (1.29) 4.08 (1.09)	- -	- -	<0.001, for time change 0.030, idem
Leveille et al. [56]	RCT (N = 201)	PACE	5.60 (N.R.)	N.R.	4.97 (N.R.)	N.R.	0.028, for group difference
Rose et al. [78]	Pretest-posttest design (N = 175)	Stretching and strengthening (Lorig) Aerobic exercise (Lorig) Cognitive symptom management (Lorig) Communication with physician (Lorig)	1.07 (1.2) 0.68 (0.9) 1.48 (1.0) 2.49 (1.4)	1.42 (1.2) 0.64 (0.7) 1.71 (1.0) 2.80 (1.0)	- - - -	- - - -	0.03, for time change >0.05, idem 0.06, idem 0.03, idem
<i>Health related quality of life</i>							
Brand et al. [65]	CCT (N = 166)	AQoL	8.7 (0.57)	N.R.	9.2 (0.48)	N.R.	>0.05, group difference
Coleman et al. [50]	RCT (N = 169)	SF-36, PCS	47.7 (N.R.)	37.5 (N.R.)	43.8 (N.R.)	37.5 (N.R.)	0.97, for group difference
Counsell et al. [51,52]	cRCT (N = 951)	SF-36, PCS SF-36, MCS	35.8 (10.8) 51.0 (10.2)	N.R. N.R.	36.5 (11.2) 51.7 (10.4)	N.R. N.R.	0.38, for group difference <0.001, idem
Courtney et al. [67]	RCT (N = 128)	SF-12, PCS SF-12, MCS	32.6 (10.3) 46.2 (12.7)	43.8 (9.4) 59.4 (5.1)	34.5 (10.6) 46.4 (10.6)	26.0 (9.9) 48.3 (7.7)	<0.001 <0.001
Douglas et al. [73]	RCT (N = 334)	SF-8, PCS SF-8, MCS	~44.0 N.R.	~41.0 N.R.	~44.0 N.R.	~43.0 N.R.	0.12, for group difference 0.22, idem
Duke et al. [55]	Pretest-posttest design (N = 107)	MGDS	N.R.	N.R.	-	-	N.R.

Elzen et al. [77]	RCT (N= 144)	RAND-36, PCS RAND-36, MCS	N.R. N.R.	N.R. N.R.	N.R. N.R.	N.R. N.R.	>0.05, for group difference >0.05, idem
Kobb et al. [40] Krause et al. [64]	CCT (N= 1401) Pretest-posttest design (N= 39)	SF-36 SF-36 (physical functioning subscale)	2.46 (1.02)	2.85 (0.81)	-	-	Not tested for significance 0.020, for time change
Leveille et al. [56]	RCT (N= 201)	SF-36 (physical function subscale) SF-36 (role limitations caused by physical health problems subscale) SF-36 (role limitations caused by emotional health problems subscale) SF-36 (general health subscale)	66.4 (22.7) 53.2 (40.9) 70.6 (40.1) 66.2 (17.4)	N.R. N.R. N.R. N.R.	62.9 (22.7) 50.0 (42.2) 76.1 (36.6) 64.4 (19.2)	N.R. N.R. N.R. N.R.	0.461, for group difference 0.610, idem 0.530, idem 0.751, idem
Markle – Reid et al. [58]	RCT (N= 288)	SF-36, PCS SF-36, MCS	37.9 (17.8) 54.3 (19.5)	49.1 (24.6) 65.1 (22.4)	37.5 (17.7) 60.7 (18.7)	46.7 (23.4) 65.2 (22.1)	0.522, for group difference 0.009, idem
Mitton et al. [60]	Pretest-posttest design (N= 37)	SF-8, PCS SF-8, MCS EQSD	45.5 (N.R.) 52.0 (N.R.) N.R.	N.R. N.R. N.R.	- - -	- - -	0.314, for time change 0.968, idem N.R.
Naylor et al. [74]	RCT (N= 239)	MLHFQ MLHFQ (physical dimension) MLHFQ (emotional dimension)	2.4 (0.7) 2.8 (0.9) 3.3 (1.3)	2.8 (1.8) 3.1 (1.9) 3.1 (1.9)	2.3 (0.7) 2.8 (0.9) 3.3 (1.2)	2.6 (1.7) 2.9 (1.9) 3.0 (1.9)	>0.10, for group difference >0.10, idem >0.10, idem
Rose et al. [78]	Pretest-posttest design (N= 175)	Modified version of HAQ and SF-36: Self-rated health Disability Social/role activities/limitations Pain Illness intrusiveness Energy/fatigue Health distress Shortness of breath	3.5 (0.8) 0.4 (0.6) 1.4 (1.3) 4.8 (3.4) 33.0 (16.9) 3.2 (1.0) 1.7 (1.3) 3.3 (3.1)	3.4 (0.7) 0.4 (0.5) 1.2 (1.1) 4.5 (3.5) 33.3 (17.5) 3.0 (0.8) 1.6 (1.2) 3.3 (3.3)	- - - - - - - -	- - - - - - - -	For time change >0.05 >0.05 >0.05 >0.05 >0.05 0.04 >0.05 >0.05
Rubenstein et al. [61]	RCT (N= 792)	SF-36 (general health perception subscale) SF-36	33.5 (13.8)	35.6 (13.5)	33.7 (12.4)	36.2 (13.1)	>0.05, for group difference
Taylor et al. [76]	RCT (N= 169)	DUKE	N.R.	N.R.	N.R.	N.R.	N.R.
Zhang et al. [75]	CCT (N= 65132)	Physical health Mental health Social health	27.2 (23.3) 57.8 (25.0) 61.3 (21.9)	25.9 (21.9) 56.6 (24.1) 59.1 (21.4)	33.2 (23.0) 59.3 (25.0) 62.6 (22.9)	31.1 (25.0) 51.8 (24.3) 21.6 (21.6)	For group difference >0.05 <0.01 <0.01

Table 3a (Continued)

Study	Study design (N) ^a	Measuring instrument ^b	Comprehensive care group ^c		Usual care group		p
			Baseline	Follow-up	Baseline	Follow-up	
		General health	48.4 (18.6)	46.9 (17.6)	51.3 (19.5)	47.4 (19.1)	<0.05
		Perceived health	26.7 (35.1)	23.8 (32.9)	35.7 (38.8)	29.5 (38.4)	<0.05
		Self-esteem	72.6 (22.9)	70.4 (22.5)	71.8 (23.3)	67.6 (23.3)	<0.05
		Anxiety	50.6 (23.0)	52.0 (22.2)	48.5 (21.8)	51.9 (22.2)	<0.05
		Depression	52.5 (24.0)	53.5 (22.8)	49.1 (24.3)	55.2 (23.8)	<0.01
		Anxiety/depression	50.1 (23.7)	51.3 (22.9)	47.3 (23.9)	52.6 (23.0)	<0.01
		Pain	74.2 (32.1)	76.5 (31.5)	64.2 (34.3)	69.0 (34.4)	>0.05
		Disability	27.6 (25.4)	27.7 (25.4)	24.1 (25.1)	28.1 (25.6)	<0.01
Medication use							
Burns et al. [66]	RCT (N= 130)	N.R.	6.2 (3.3)	5.8 (3.8)	6.9 (3.3)	7.2 (3.5)	<0.01, for group difference >0.05, for time change >0.05, for interaction
Coleman et al. [50]	RCT (N= 169)	Use of high risk medication (Pharmacy database)	2.0 (N.R.)	1.9 (N.R.)	3.9 (N.R.)	2.5 (N.R.)	0.20, for group difference
Kobb et al. [40]	CCT (N= 1401)	Prescription refills and information of patients and informal caregivers	-	Medication compliance increased from 68% to 93%	-	-	Not tested for significance
Schmader et al. [70]	RCT (N= 864)	Inpatient period No. of unnecessary drugs Medication appropriateness (medication appropriateness index) No. of inappropriate drugs No. of conditions with omitted drugs Outpatient period No. of unnecessary drugs Medication appropriateness (medication appropriateness index) No. of inappropriate drugs No. of conditions with omitted drugs	0.9 (1.1) 10.0 (7.8) 0.5 (0.7) 1.4 (1.3) 0.7 (1.0) 7.5 (7.3) 0.3 (0.6) 1.0 (1.1)	0.4 (0.7) 5.3 (4.9) 0.2 (0.5) (1.1) 0.7 (1.0) 7.6 (7.9) 0.3 (0.5) 0.8 (0.9)	0.7 (0.9) 7.7 (7.2) 0.5 (0.7) (1.1) 0.6 (0.9) 7.5 (6.9) 0.3 (0.6) 1.1 (1.2)	0.8 (1.1) 9.6 (8.2) 0.4 (0.6) 1.1 (1.3) 0.7 (0.9) 8.3 (6.6) 0.3 (0.5) 1.2 (1.3)	Group difference <0.0001 <0.0001 0.03 <0.0001 0.47 0.26 0.78 0.0004
Sorrento et al. [62]	Pretest-posttest design (N= 273)	DAM	N.R.	N.R.	-	-	Not tested for significance

^a For these tables we used information that was provided in the original papers. In several papers, however, information was not complete, which explains why baseline, follow-up, and/or p-values are sometimes missing. It should further be noted that outcomes related to patient satisfaction and quality of care are not included in these tables since they were mostly measured in a qualitative way. For the same reason informal caregiver and professional caregiver related outcomes are not included either.

Table 3b
Clinical patient outcomes of studies evaluating impact of comprehensive care programs for multimorbid patients.*

Study	Study design (N) ^a	Measuring instrument ^b	Comprehensive care group ^c		Usual care group ^c		p
			Baseline N or %	Follow-up N or %	Baseline N or %	Follow-up N or %	
<i>Medication use</i> Tibaldi et al. [71]	RCT (N= 109)	Number of patients using antipsychotic drugs	N = 26	N = 6	N = 17	N = 13	0.001, for group difference
<i>Mortality</i> Counsell et al. [51,52]	cRCT (N= 951)	Number of deaths	-	N = 33	-	N = 37	0.64, for group difference
Dorr et al. [53,54]	CCT (N= 3432, of whom 1671 had complex illness including diabetes)	Rate of deaths <i>All patients with complex illness</i> <i>Patients with complex illness including diabetes</i>	-	13.1% N.R.	-	16.6% N.R.	0.07, for group difference 0.03, idem
Douglas et al. [73]	RCT (N= 334)	Number of deaths	-	N.R.	-	N.R.	>0.05, for group difference
Naylor et al. [74]	RCT (N= 239)	Number of deaths	-	N = 11	-	N = 13	0.830, for group difference
Saltvedt et al. [68,69]	RCT (N= 254)	Number of deaths	-	N = 35	-	N = 43	>0.05, for group difference
Tibaldi et al. [71]	RCT (N= 109)	Number of deaths	N.R.	N.R.	N.R.	N.R.	>0.05, for group difference

^a CCT = controlled clinical trial; cRCT = cluster-randomized controlled trial; RCT = randomized controlled trial.

^b ADL = Activities of Daily Living; AHEAD = Assets and Health Dynamics of the Oldest-Old; AQoL = Assessment of Quality of Life Instrument; BDI = Beck Depression Inventory; CES-D = Centre for Epidemiologic Studies Depression Scale; DAM = Drug Appropriateness Measure; DUKE = Duke Health Profile; EQ5D = A measure of health status of the EuroQol Group; ESDS = Enforces Social Dependency Scale; FIM = Functional Independence Measure; FSQ = Functional Status Questionnaire; GDS = Geriatric Depression Scale; HAQ = Health Assessment Questionnaire; IADL = instrumental activities of daily living; MADRS = Montgomery Asberg Depression Rating Scale; MCS = Mental Component Scale; MGDS = Modified Geriatric Depression Scale; MLHFQ = Minnesota Living with Heart Failure Questionnaire; MMSE = Mini Mental State Examination; N.R. = not reported OASIS = Outcomes and Assessment Information Set; PACE = Physician-based Assessment and Counseling for Exercise scoring form; PCS = Physical Component Scale PPCQ = Perception of Personal Control Questionnaire; SF-8, SF-12, SF-36 = Medical Outcomes 8-item, 12-item, and 36-item short-form.

^c N.R. = not reported.

* For these tables we used information that was provided in the original papers. In several papers, however, information was not complete, which explains why baseline, follow-up, and/or p-values are sometimes missing. It should further be noted that outcomes related to patient satisfaction and quality of care are not included in these tables since they were mostly measured in a qualitative way. For the same reason informal caregiver and professional caregiver related outcomes are not included either.