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The effect of physician-nurse substitution in primary care in chronic diseases: a systematic review

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Summary

BACKGROUND: Chronically ill and ageing populations demand increasing human resources who can provide ongoing and frequent follow-up care. We performed a systematic review to assess the effect of physician-nurse substitution on process care outcomes.

METHODS: We searched OVID Medline, Embase, CINAHL and The Cochrane Library for all available dates up to August 2012 and updated in February 2014. We selected and critically appraised published randomised controlled trials (RCT) and followed the PRISMA guidelines for the reporting of systematic reviews.

RESULTS: A total of 14 RCTs comprising 10,743 participants met the inclusion criteria. Studies were generally small and suffered from attrition of ≥20% and selection biases. There were 53 process measurements investigated in the 14 RCTs, many of which were unique to specific conditions. Accounts of nurses' roles, responsibilities, tasks, qualifications and training content/components were not described in sufficient detail. Most study estimates showed no significant differences between nurse-led care and physician-led care while less than a half (~40%) favoured nurse-led care.

CONCLUSIONS: Despite the methodological limitations and the varying nurses' roles and competencies across studies, specially trained nurses can provide care that is at least as equivalent to care provided by physicians for the management of chronic diseases, in terms of process of care. Future, larger studies with better quality methods are needed and should report and assess whether the differences in effects vary due to diversity in roles, qualifications, training competencies and characteristics of clinicians delivering substitution of care.

Key words: *systematic review; physician-nurse substitution; primary healthcare; chronic disease; delivery of healthcare; process indicators*

Introduction

The need for healthcare services is becoming more heterogeneous as the burden of chronic diseases and population ageing spreads rapidly. Chronically ill and ageing populations are expected to rise as the main users of healthcare services until at least mid-twenty-first century. Consequently, these populations are bound to have more extended care needs (including psychosocial and behavioural support) and an increased demand for human resources. A WHO report however, showed the global number of health care providers, namely physicians, nurses and midwives, remains lower than required per 1,000 population [1–3]. By 2011, 57 countries were still facing a critical shortage of these health workers including regions in Africa, Eastern Mediterranean, South-East Asia, Western Pacific, Americas and Europe [4]. Factors greatly contributing to this shortage include the low flow of primary care physicians (less graduates selecting and remaining in the primary care sector), changes in the working culture (e.g. newer generations of physicians working fewer hours than prior generations) and trends in retirement [5]. These changes have provided plenty of opportunities to create innovative staff-mix models [6].

It has long been suggested that nurses should perform greater roles and be granted full practice [7]. Indeed, nurses already provide an increasingly important contribution in primary care and although decreasing in number, they are still one of the largest groups of qualified healthcare professionals and they are also less expensive than physicians. Therefore their role for substituting physicians has gained increasing interest from policymakers hoping to address workforce shortages and maldistribution of workload, while reducing costs, especially in the care for the chronically ill [2, 8]. However at this time, it has been difficult to demonstrate how best to integrate nurses in a substitution model of care. Especially with the variability in definitions of nurses' roles and the diversity of competencies among roles with the same name or differing roles and skills among healthcare systems, this integration may seem doubtful. Nevertheless, nurses' education keeps evolving in order to adjust to new demands in healthcare and nurses continue to support physicians in many areas in many countries. Substitution may take place in a wide range of care settings and/or clinical areas. It involves the transfer of tasks which are traditionally from the domain of physicians, to nurses who then take autonomous or delegated responsibilities to deliver care.

In 2002 and 2005, two systematic reviews explored the substitution of physicians by nurses in primary care and

concluded with no appreciable differences between nurse-led care and physician-led care in terms of health outcomes (patient satisfaction, quality of life, other morbidity), use of resources and healthcare costs [9, 10]. However, authors found insufficient data on process outcomes other than length of consultations, amount of prescriptions and investigations, consultations and referrals. The identified evidence also had methodological limitations and lacked clear reporting of nurses' roles (qualifications and training) and on the use of guidelines. We performed a timely update of previous reviews [9, 10] with a focus on the process of care outcomes, other than those examined in the mentioned reviews, and on the type and degree of nurses' competencies.

Methods

This study was part of a large systematic review and meta-analysis project designed to assess the evidence of physician-nurse substitution in primary care. The methodological procedures of this systematic review are similar to those employed in the reviews of this project reported elsewhere [11]. We developed a protocol prior to the commencement of the review and followed the PRISMA guidelines [12] for the reporting of systematic reviews and meta-analyses (additional file, table S1).

Study inclusion and exclusion criteria

We searched for peer reviewed randomised or quasi-randomised (e.g., controlled before-and-after studies, interrupted time series) controlled trials (RCTs) published in English. Studies were eligible if they fulfilled the following criteria: examined populations of all ages and all conditions including mental health and addiction restricted to primary care; assigned patients to nurse-led care (all nurse roles) or physician-led care (family physicians, paediatricians and geriatricians) based on a substitution model; and if care interventions had taken place in general practices, community or ambulatory care settings regardless of the recruitment sources. We further limited the inclusion of studies to the report of process of care outcomes, which meant measures that reflected whether clinicians performed certain steps in diagnostic and treatments that are considered to be state of the art based on guidelines or good clinical practice (e.g. specific examinations/diagnostic tests, compliance with monitoring schemes). Following a framework published by a Cochrane review [10], we excluded studies in which nurses supplemented (i.e. complemented or extended care) the work of physicians or in which the effect of nurse-led care could not be distinguished from collaborative teams. We excluded measures of quality of life, satisfaction, mortality, hospital admissions, progression of disease and other clinical parameters.

Study identification and search strategy

We comprehensively searched OVID Medline, Embase, CINAHL and The Cochrane Library which includes the Cochrane Effective Practice and Organization of Care Group (EPOC). The original search was supported by an expert librarian. All searches were first performed for all available dates until August 2012. The searches were not restricted by age, date or country and included terms for 'primary care', 'skill mix', 'doctors', 'nurse', 'substitution' (additional file, table S2). We identified additional studies by manual searching of the reference lists of included studies and relevant reviews. Both electronic and manual searches were updated in February 2014.

Assessment of study quality

In view of the continuing debate about scoring the quality of trials, discussed by Juni et al. (1999) [13], a composite score was not performed. We assessed the risk of bias of individual trials following established criteria [14, 15] and provide a description of the studies' adequacy regarding each item and an overall judgment of the quality of evidence. We considered bias due to attrition of at least 20% to be of significant concern and adequate intention-to-treat (ITT) when authors analysed participants based on their original group allocation [16].

Selection and assessment of studies

Two authors independently screened titles and abstracts, assessed the full-text of eligible publications and the risk of bias of included studies. Differences were resolved in discussion or by consensus with another author.

Data extraction

Two authors independently conducted data abstraction using *a-priori* designed and standardised data collection forms. We extracted information on bibliographic details, settings and characteristics of populations, interventions (nurses' training competency and role, type of care, whether nurses were granted full clinical autonomy and whether interventions were delivered following specific protocols or guidelines, length of follow-up) and outcomes. Using the description of interventions and qualifications reported by study authors we grouped nurses' training and roles into: nurse practitioner (NP) or nurse practitioner (NP+) who took or already had -for the purposes of the study- higher degree courses or had a specialisation; registered nurse (RN) or licensed nurse (LN). We also extracted quantitative and semi-quantitative data in dichotomous and/or continuous format. Data from trials reported across more than one publication were extracted as one study. If trials reported more than one comparison group of interest (e.g. family physicians and paediatricians), data were combined and compared as one to nurse-led care. We did not contact study authors to obtain additional information or data. Differences were resolved through consensus.

Statistical analyses

There was mostly one study per outcome thus we did not perform meta-analyses nor did we pre-specify subgroup analyses by clinical or methodological (risk of bias) characteristics. Where data were sufficiently reported, for each study outcome we calculated the unadjusted relative risks (RR) or the standard mean differences (SMD) and 95% confidence intervals (CI) of the absolute endpoints, using Review Manager (Version 5.1) [17]. We considered $p < 0.05$ as statisticaly significant. The calculated effect sizes were tabulated with information on nurses' roles and studies were arranged, within outcome categories, in increasing length of follow-up. The results were synthesised qualitat-

ively. When scales pointed in opposite directions, we subtracted the mean from the maximum possible value of the scale or multiplied the mean of a set of studies by –1. We followed reported techniques to estimate standard deviations (SD) when these were missing [15]: using the information from the reported statistical analyses (e.g. from median and interquartile ranges), and if SDs of the final measurements were unavailable, we carried forward the baseline SDs assuming the intervention did not alter the variability of the outcome. Medians were treated differently from means and are reported distinguishably.

Results

Study identification

A total of 4,589 original records were identified by the electronic and manual searches. Of these, 44 publications were relevant, but 24 were excluded for the reasons provided in table S3 (additional file). Finally, 14 RCTs reported in 20 publications, met the inclusion criteria and comprised a total of 10,743 randomised participants [18–37]. Figure 1 shows the process of study selection.

Study and population characteristics

Table 1 and table S4 (additional file) show the study and population characteristics of included studies. All RCTs individually assigned participants to intervention and control groups and were conducted in the UK (n = 6), the Netherlands (n = 5), the USA (n = 2), and Russia (n = 1). Median follow-up was 12 (range 0.5 to 48) months with at least 12 months in 7 trials and less than 12 months in the other 7. The number of participants ranged from 60 to 1,859 with less than 200 (range 60 to 175) in six trials and more than 200 (range 230 to 1,859) in the other eight. Age was reported in twelve trials. Mean age ranged from 11.2 (SD 2.9) to 69.5 (SD 10.6) years in ten trials and age ranged from 0 to 83 in other two. In 13 RCTs that reported on gender, 49% of the population were male (range: 27 to 64%).

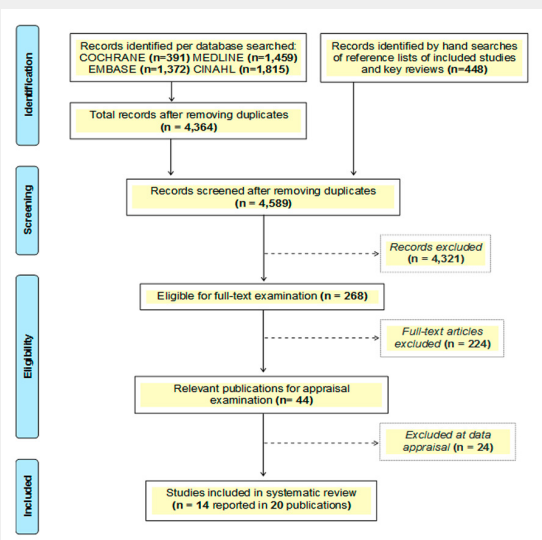

Figure 1

Flow diagram – study selection process.

Settings and interventions

Table 2 and table S4 (additional file) report the characteristics of settings and interventions. Nurses worked as physician substitutes in physicians' practices, nurse clinics, hospital outpatient clinics, reference clinics, and medical health centres. A total of 10 trials reported the number of participating nurses and/or physicians. In ten, the median number of nurses was 7.5 (range: 2 to 28) while in seven, the median number of physicians was 14 (range: 5 to 50). The location of practices (rural or urban) and social settings were scarcely reported. Nurses delivered care for a wide range of possible (diverse/undifferentiated/minor acute/common) or specific conditions (e.g. hypertension, heart failure, diabetes, HIV, etc.). Care provided ranged from single contact care, on-going care, first contact only care, first contact and on-going care, and first contact for urgent care. Only four trials [25, 27, 30, 36] reported the nurses' years of experience (range: 0.17 to 12) and only one [25] reported that physicians had 16 years of experience. Nine trials employed NPs (NPs or NP+), and the rest employed LNs and/or RNs and/or NPs. Nurses were either enrolled as staff, took courses or already had professional qualifications by the time of participating in the study. Unfortunately, the educational preparation of nurses was reported insufficiently. Only four studies specifically stated that nurses had obtained an academic degree either a Masters in Advance Nursing [25], a Diploma in General Practice and implied an NP degree [30], a special degree in patient education [18], or had done a degree level course [36]. The terminology used by study authors to refer to participating nurses in the studies did not provide a straightforward definition of the various nurses' educational degrees from the countries, at least for the UK, Netherlands and Russia. For example, a NP in the US requires a graduate degree whereas the UK did not seem to have a minimum educational requirement until this was recommended in 2012 for advanced NPs [38]. A "hypertension nurse" may then refer to a NP or a practice nurse both of whom are specialists in hypertension but each of whom might hold different educational degrees, for example basic education at diploma or degree level plus/or a bachelor's or a master's degree. The content of training or experience was often not described in detail. The lack of this information impeded a detailed assessment of the level of education and competencies, and the identification of common components across trials. All studies however, seem to assume that nurses fulfilled the appropriate clinical competency to deliver the study interventions. Responsibilities and tasks also varied across trials and were often incomplete. Nurses had full clinical autonomy in only two trials: one in patients with undifferentiated conditions [26] and one in diabetic patients [28]. In the remaining trials, nurses independently performed several tasks, but they still needed minor support from physicians, for example to report findings, sign prescriptions, referrals and hospitalisations, or to discuss patients' records. Ten trials reported nurses' interventions followed specific guidelines or protocols.

Risk of bias in the methods of the included studies

The overall quality of studies varied substantially when assessed against current reporting standards [14] (table 3). In-

clusion and exclusion criteria were reported in 71% of the trials and funding sources in 64% of the trials. The success of the intervention was measured by defining a primary outcome in 50%. Among all trials, random sequence generation was adequate in 57%, allocation concealment in 50% and both criteria were adequate in 43%. No trial blinded both patients and providers. Patients were blinded in one trial, and outcome assessors were blinded in 36%. Patient or clinician crossover between groups was reported in two trials. Sample size calculation (80 to 90% power) was performed in 79% of the trials but only five maintained the required sample to achieve power. At baseline, patient groups were comparable for all tested factors in 71%. Attrition rate was ≥20% in 43%. Missing data (range 5 to 42%) was dealt with intention to treat (ITT) techniques in 29%.

Effectiveness of interventions

We identified 53 measurements of process of care reported in the 14 RCTs. Of these, 34 were reported in ten trials in which nurses cared for patients with specific conditions. The other 19 process of care measures were reported in four trials in which nurses cared for patients with more general conditions. Table 4 and table 5 show the individual trial estimates calculated from reported data.

Adherence to practical guidelines

Adherence of clinicians to practical guidelines was non-significant between groups in one trial [25].

Blood pressure management according to guidelines

Blood pressure management according to guidelines showed significantly more patients in the nurse group, compared to physicians, met a composite target (SBP and

Table 1: Summary of study and population characteristics of studies included in review.

Study			Participants	Nurse group				Physician group			
First author, publication (y)	**Location**	**Design, period***	**diagnosis**	**Nurses (n)**	**Patients (n)**	**Mean age (SD), years**	**Male, %**	**Physicians (n)**	**Patients (n)**	**Mean age (SD), years**	**Male, %**
Houweling et al. 2011	NL 5	RCT, period NR	DM2	2	116	67.1 (11)	53	5	114	69.5 (10.6)	42
Kuethe et al. 2011	NL 4	RCT, 2006–2008	Asthma	NR	36	11.2 (2.9)	64	NR	71	11.2 (2.5)† 10.1 (2.6)‡	58
Voogdt-Pruis et al. 2010	NL 3	RCT, 2006–2007	CVD, hypertension, hypercholesterolaemia	6	808	64 (9.0)	58	25	818	64 (9.0)	62
Andryukhin et al. 2010	RU 1	RCT, 2006 -2009	Heart failure with preserved ejection fraction	10	50	66.5 (3.2)	27	8	50	68 (4.3)	34
Dierick-Van Daele et al. 2009	NL 2	RCT, 2006	Common complaints	12	817	42.8 (16.5)	38	50/17§	684	46.1 (16.6)	40
Chan et al. 2009	UK 6	RCT, 2002–2004	GORD, moderate gastritis	NR	89	50.2 (13.9)	49	NR	86	48.4 (12.8)	49
Hesselink et al. 2004	NL 1	RCT, 1998–2002	Asthma and COPD	2	139	49.9 (14.2)	35	14	137	44.7 (13.6)	28
Denver et al. 2003	UK 5	RCT, 2000–2001	DM2, hypertension, under blood pressure lowering treatment	NR	60	58.1 (13.8)	57	NR	60	62.4 (9.1)	70
Jarman et al. 2002	UK 4	RCT, 1996–1999	Parkinson's disease	9	1041	NR	57	NR	818	NR	56
Kinnersley et al. 2000	UK 3	RCT, period NR	Diverse	12	1465¶	Range: 0 to >75	39	10	1465¶	Range: 0–>75	42
Shum et al. 2000	UK 2	RCT, 1998–1999	Acute minor illnesses	5	900	Median (IQR): 26 (9–41.8)	40	19	915	Median (IQR): 29.1 (9.7–44.9)	40
Campbell et al. 1998	UK 1	RCT, 1995–1996	CHD secondary prevention	28	673	66.1 (8.2)	58	NR	670	66.3 (8.2)	58
Flynn et al. 1974	US 2	RCT, 1971	Undifferentiated	4	40	NR	NR	NR	20	NR	NR
Lewis et al. 1967	US 1	RCT, period NR	Hypertension, CVD, obesity, arthritis, somatisation	NR	33	Range: 16–78	12	NR	33	Range: 16–83	12

Studies are listed by year (y) of publication, in decreasing order.
NL = The Netherlands; UK = United Kingdom; US = United States; RU = Russia; NR = not reported; DM(2) = diabetes mellitus (type 2); GORD = gastro-oesophageal reflux disease; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease; SD = standard deviation.
* Start and end year when studies were conducted
† General physicians
‡ Paediatricians
§ Reference practices for comparison on economic/cost data
¶ Number of randomised patients per group not reported

Table 2: Summary characteristics of settings and interventions of studies included in review.

Study		Setting/ Facilities, n	Disease	Intervention							
First author, publication (y)	**Location**		**diagnosis**	**Delivered by**	**Training/ competency**	**FCA**	**GDL**	**1st C**	**UV**	**OC**	**C, n**	**FUP, m**
Houweling et al. 2011	NL 5	Practice, 1	DM2	NP	Practice nurse with one week training in diabetes mellitus; nurse had no special training in the treatment of diabetes prior to starting trial	Yes	Yes	No	No	Yes	>1	14
Kuethe et al. 2011	NL 4	HO, 1; Practice, 18	Asthma	NP+	Asthma nurse	No	Yes	No	No	Yes	>1	24
Voogdt-Pruis et al. 2010	NL 3	Healthcare centre, 6	CVD, Hypertension, Hypercholesterolaemia	NP+	Advance practice nurse already employed to manage patients with asthma, chronic obstructive pulmonary disease, or diabetes	NR	Yes	No	No	Yes	>1	12
Andryukhin et al. 2010	RU 1	Medical center practice, 1.	Heart Failure with preserved ejection fraction	NP/LN	Nurses with special degree in patient education obtained in a joint course	No	Yes	No	No	Yes	>1	6
Dierick-Van Daele et al. 2009	NL 2	Practice, 15; Reference, 5	Common complaints	NP+	Nurse practitioner with Masters in Advance Nursing trained in common complaints	No	Yes	Yes	No	No	1	0.5, AC
Chan et al. 2009	UK 6	Nurse clinic, 1	GORD, moderate gastritis	NP+	Gastrointestinal nurse practitioner	No	Yes	No	No	Yes	>1	6
Hesselink et al. 2004	NL 1	Practice, 12	Asthma and COPD	LN	GP assistant with pre- and during-trial training to deal with the differences between asthma and COPD	No	Yes*	No	No	Yes	>1	12, 24
Denver et al. 2003	UK 5	Nurse HB Hypertension clinic, n = NR	DM2, hypertension, under blood pressure lowering treatment	NP+	Hypertension nurse	No	Yes	No	No	Yes	>1	6
Jarman et al. 2002	UK 4	Practice, 438	Parkinson's disease	LN	Community nurse with a course in Parkinson disease	No	NR	No	No	Yes	>1	24
Kinnersley et al. 2000	UK 3	Practice, 10	Diverse	NP	Nurse practitioners with diploma on care for same day consultations for primary care	No	NR	Yes	Yes	No	1	AC, 0.5
Shum et al. 2000	UK 2	Practice, 5	Acute minor illnesses	NP	Practice nurse with no specific experience in minor illnesses but with a course in management of minor illnesses and were piloted before starting study	No	NR	Yes	Yes	No	≥1	0.5 –1

Campbell et al. 1998	UK 1	Practice, 19	CHD secondary prevention	NP	District and practice nurses trained in clinic protocols/GDLs for behavioural techniques change	No	Yes	No	No	Yes	>1	12, 48
Flynn et al. 1974	US 2	HO clinic, 1; Private, 3	Undifferentiated	RN	Nurse clinicians with training in service delivery including health status, quantity and efficiency of care	Yes	NR	Yes	No	Yes	>1	6–12
Lewis et al. 1967	US 1	UH clinic, 1; Nurse clinic, 1	Hypertension, CVD, obesity, arthritis, somatization	LN	Nurses who provided primary source care for at least one year before the study	No	Yes	No	No	Yes	>1	12

Studies are listed by year (y) of publication, in decreasing order.
NL, = The Netherlands; UK = United Kingdom; US = United States; RU = Russia; NR = not reported; DM(2) = diabetes mellitus (type 2); GORD = gastro-oesophageal reflux disease; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; NP = nurse practitioner; NP+ = nurse practitioner with higher degree/course; RN = registered nurse; LN = licensed nurse; FCA = full clinical autonomy; GDLs = whether interventions guidelines or protocol based; 1st C = 1st contact; UV = urgent visits; OC = on-going care; C(n) = number of consultations; FUP = follow-up episodes in months; NR = not reported; AC = after consultation.

DPB, mm Hg: RR 1.1, 95% CI 1.06 to 1.13, p <0.00001) [20] and systolic blood pressure target (SBP, mm Hg RR 3.14, 95% CI 1.38 to 7.19, p = 0.007) [24]. However, the effect did not sustain at 48 [20] or 14 months [28] and was non-significant for DPB only [24].

Lipids

Significantly more patients in nurse-led care, compared to physicians, had appropriate secondary prevention of heart disease through the adequate management of lipids at 12 months following specific guidelines in one trial (RR 1.91, 95% CI 1.59 to 2.29, p <0.00001) [20]. However, these differences were non-significant at 14 or 48 months.

HbA1c

One trial showed no significant differences between nurse-led care and physician-led care in the number of patients who met the target values of glycated haemoglobin (HbA1c) according to guidelines for the management of diabetes mellitus type 2 at 14 months (HbA1c <7.0 or HbA1c ≤8.5) [28].

BMI and waist circumference

In one trial, compared to the physicians group, there were significantly more patients in the nurse group who had a decrease or regression in body mass index (BMI) at 6 months (RR 1.51, 95% CI 1.05 to 2.17, p = 0.03) [18] but the mean differences between groups at 12 or 14 months were non-significant in other two trials [28, 37]. One of

Table 3: Summary of risk of bias in the included studies.

Study, first author	Country	Inclusion & exclusion criteria	Outcome		Sequence generation	Allocation concealment	Blinding	Sample size	Attrition, %	Funding
			1ry	2ry						
Houweling et al. 2011	NL 5	?	?	?	I	A	NP	?	<20	G
Kuethe et al. 2011	NL 4	?	?		A	A	NP	?	<20	NR
Voogdt-Pruis et al. 2010	NL 3	?	?		A	U	I‡	?	<20	P/Ind.
Andryukhin et al. 2010	RU 1	?			U	I	†	?	≥20	None
Dierick-Van Daele et al. 2009	NL 2	?			A	A	NP	NP	≥20	G
Chan et al. 2009	UK 6	?			A	A	†	?	<20§	NR
Hesselink et al. 2004	NL 1	*	?	?	U	U	†	?	≥20	NR
Denver et al. 2003	UK 5	*	?	?	I	I	NP	?	<20§	NR
Jarman et al. 2002	UK 4	?	?	?	A	A	NP	?	<20	P/Ind.
Kinnersley et al. 2000	UK 3	?	?	?	A	A	NP	?	≥20	G
Shum et al. 2000	UK 2	?			A	A	NP	?	≥20	G
Campbell et al. 1998	UK 1	?			A	I	†	?	≥20§	G
Flynn et al. 1974	US 2	*			U	U	NP	NR	<20	NR
Lewis et al. 1967	US 1	*			U	U	†	NR	U§	G

Studies are listed by year (y) of publication, in decreasing order.
Blinding: whether patients, care providers and outcome assessors were blinded. Attrition of ≥20% is of significant concern. A tick indicates the specific criteria fulfilled. I = inadequate; A = adequate; U = unclear; NP = not performed; NR = not reported; NL = The Netherlands; UK = United Kingdom; US = United States; RU = Russia; funding: government (G), industry (Ind.) or private (P) grant.
* Only inclusion criteria was reported
† Trials with blinding of outcome assessors for all or some outcomes
‡ Only patients were blinded
§ Performed intention to treat (ITT) strategies to deal with missing data

these also showed significantly more patients in the nurse group who had a decrease or regression in waist circumference at 6 months (RR 2.36, 95% CI 1.34 to 4.16, p = 0.003) [18].

Asthma

Individual point estimates of one trial showed, compared to physician-led care, significantly more patients with a correct inhalation technique at 12 months in the nurse-led care group (RR 1.33, 95% CI 1.01 to 1.74, p = 0.04) [27], but the effect was non-significant at 24 months. In another trial, the differences between groups in the number of patients with well-controlled asthma were non-significant at 12 or 24 months [31].

Feet at risk

Compared to patients in physician-led care, there were significantly less patients with feet-not-at-risk in the nurse-led care group (of the patients who underwent measures to prevent the development of diabetic foot symptoms) (RR 0.59, 95% CI 0.42 to 0.82, p = 0.002) [28].

Visuomotor coordination

There was a significant improvement in best hand score in patients with nurse-led care, compared to patients in the physicians group in patients with Parkinson's disease in one trial (MD –4.31, 95% CI –4.52 to –4.11, p <0.00001) [29].

Appropriate secondary prevention

Individual point estimates from one trial [20] showed significantly more patients with nurse-led care, compared to physician-led care, had appropriate secondary prevention of heart disease through the adequate management of aspirin intake (taken or contraindicated) (RR 1.22, 95% CI 1.14 to 1.31, p <0.00001) or low-fat diet (RR 1.16, 95% CI 1.03 to 1.31, p = 0.02) or moderate physical activity (RR 1.35, 95% CI 1.16 to 1.58, p = 0.0001) at 12 months. However, the effect did not sustain at 48 months except for moderate physical activity (RR 1.23, 95% CI 1.02 to 1.49, p = 0.03). Conversely, there were no significant differences between groups in the number of patients who had appropriate secondary prevention of heart disease through non-smoking at 12 or 48 months [20] or smoking cessation for asthma/COPD at 24 months in one trial [27].

Adherence to treatment, correct medication and diet

Adherence to treatment (in patients under anti-inflammatory agents) was non-significant between groups neither at 12 nor at 24 months in one trial [27]. Another trial showed a marginal significance that favoured the nurse-led care group in the number of patients who adhered to milk as part of their nutritional diet (RR 0.62, 95% CI 0.38 to 1, p = 0.05) [26] but no significant differences between groups in the number of patients who adhered to a special diet, bread taking, or with correct medication, at 6–12 months.

Patient information and knowledge

Seven trials reported on various types of provision of information, advice from clinicians or patient knowledge. There were generally one or two trials per outcome type. Nurses provided significantly more information than physicians on the causes of health problems or illness [22, 30] in two of the three trials with these data. Nurses also gave significantly more advice about relief of symptoms, duration of illness, how to reduce recurrences and what to do if problems persisted in one [30] of two trials [25, 30]; as well as more advice on self-medication and self-management [36], special exercises [26], and provided leaflets about patients illness [22]. Patients' knowledge about the complications of disease was non-significant between groups [26]. In another trial, although data was collected, results were not reported [32].

There was no evidence of worsening outcomes with nurse-led care compared to physician-led care.

Discussion

Substitution of physicians by nurses has increased the possibility of achieving the quality outcomes required to satisfy the demands of an aging population and the shortages of physicians in many countries. We found however that the number of studies in this area is only increasing slowly despite previous reports [9, 10]. The studies were generally small and none fulfilled all quality criteria. More than 40% of the studies suffered from selection (lack/unclear allocation concealment and random generation) and attrition (≥20%) biases, and very probable publication bias since our review was limited to the published literature. Only a few studies maintained the sample required to achieve power and the length of follow up varied widely. It may not be surprising that most of the evaluated trials were conducted in Europe, mainly the UK, and the Netherlands. In the USA and Canada medical care has evolved to a shared role since NPs and physicians' assistants were introduced or reinvigorated, both in the mid-1960s [39]. However, the USA is still in great need of more nurses to level out the shortage of primary care physicians [40, 41]. In the UK on the other hand, the introduction of nurses in advanced roles did not happen until early 1970s and the role of NPs were not consolidated until 1990 [42].

The studies generally assessed a large variety of process of care outcomes, sometimes with many unique measurements per study but only 38.3% (13/34) of those taken in patients with specific conditions and 42.1% (8/19) related to general conditions, significantly favoured nurse-led care compared to physicians. The remaining studies showed non-significant differences.

The competencies to treat the elderly and the chronically ill may differ among different types of nurses or physicians. Research has reported a reduction in mortality, failure-to-rescue rates, ulcers and length of stay after increasing the proportion of nurses who possess a bachelor's degree [43–47]. However, unless stated by study authors, the evaluated literature does not offer sufficiently reported details on nurses' educational level. The literature reflects an overuse of terminology for nurses' job titles. In addition, nurses' qualifications did not seem consistent among these, although nurses had received training to deliver the interventions. Nor was it possible to make clear judgments about nurses' educational level by using a country's definition of the terminology that authors used to refer to nurses.

Table 4: Individual trial estimates from binary data.

Reference details	Interventions, delivered by	Outcome reported	FUP, m	Nurse group, n/N	Physician group, n/N	RR (95% CI)	*p*-value
Blood pressure appropriately managed according to guidelines							
Denver et al. 2003	NP+	SBP target achieved: 140/80 mm Hg for patients without renal complications; 120/70 mm Hg for patients with renal complications	6	20/53	6/50	3.14 (1.38 to 7.19)	0.007
Denver et al. 2003	NP+	DBP target achieved:140/80 mm Hg for patients without renal complications; 120/70 mm Hg for patients with renal complications	6	30/60	22/60	1.36 (0.9 to 2.07)	0.150
Campbell et al. 1998	NP	SBP and DBP target achieved 160/90 mm Hg	12	572/593	510/580	1.1 (1.06 to 1.13)	<0.00001
Houweling et al. 2011	NP	SBP and DBP target achieved <140/90 mm Hg	14	26/102	22/104	1.2 (0.73 to 1.98)	0.460
Campbell et al. 1998	NP	SBP and DBP target achieved 160/90 mm Hg	48	530/564	492/534	1.02 (0.99 to 1.05)	0.230
Lipids appropriately managed according to guidelines							
Campbell et al. 1998	NP	Patients with appropriate secondary prevention, lipids management according to general practices: achieved target of ≤5.2 mmol/l in the last measurement for cholesterol (recorded within three years) or if lipids treated, checked within three months, or patient attending a specialist clinic	12	244/593	125/580	1.91 (1.59 to 2.29)	<0.00001
Campbell et al. 1998	NP	Patients with appropriate secondary prevention, lipids management according to general practices: achieved target of ≤5.2 mmol/l in the last measurement for cholesterol (recorded within three years) or if lipids treated, checked within three months, or patient attending a specialist clinic	48	325/564	284/534	1.08 (0.97 to 1.21)	0.140
Houweling et al. 2011	NP	Patients achieving individual target value according to guidelines: taking age and cardiovascular risk factors into account	14	81/102	88/104	0.94 (0.83 to 1.07)	0.330
Hemoglobin appropriately managed according to guidelines							
Houweling et al. 2011	NP	Haemoglobin management for the treatment of DM2 target HbA1c <7.0	14	35/102	45/104	0.79 (0.56 to 1.12)	0.190
Houweling et al. 2011	NP	Haemoglobin management for the treatment of DM2: target value for HbA1c ≤8.5	14	88/102	91/104	0.99 (0.89 to 1.1)	0.790
Feet at risk							
Houweling et al. 2011	NP	Feet not at risk: examination in whom measures were taken to prevent the development of diabetic foot symptoms	14	26/60	36/49	0.59 (0.42 to 0.82)	0.002
Asthma							
Hesselink et al. 2004	LN	Correct inhalation technique according to 10–item validated checklist: less than two negative scores	12	63/95	37/74	1.33 (1.01 to 1.74)	0.040
Hesselink et al. 2004	LN	Correct inhalation technique according to 10–item validated checklist: less than two negative scores	24	58/77	36/61	1.28 (1 to 1.63)	0.050
BMI and waist circumference							
Andryukhin et al. 2010	NP / LN	Waist circumference: positive decrease or regression	6	27/40	10/35	2.36 (1.34 to 4.16)	0.003
Andryukhin et al. 2010	NP / LN	Body mass index: decrease/regression to less than upper limit of 95% CI or stay within 30 kg/m²	6	31/40	18/35	1.51 (1.05 to 2.17)	0.030
Adherence to treatment and diet and correct medication taken							
Flynn et al. 1974	RN	Correct medication taken as an indicator of health status as perceived by the patient	6–12	32/38	12/19	1.33 (0.92 to 1.93)	0.130
Flynn et al. 1974	RN	Adherence to special diet as part of a nutritional diet as indicator of health status as perceived by the patient	6–12	8/38	6/19	0.67 (0.27 to 1.65)	0.380
Flynn et al. 1974	RN	Adherence to bread as part of a nutritional diet as indicator of health status as perceived by the patient	6–12	26/38	16/19	0.81 (0.61 to 1.09)	0.160
Flynn et al. 1974	RN	Adherence to milk as part of a nutritional diet as indicator of health status as perceived by the patient	6–12	16/38	13/19	0.62 (0.38 to 1)	0.050

Hesselink et al. 2004	LN	Improved adherence to treatment in patients under anti-inflammatory agents	12	38/63	22/44	1.21 (0.84 to 1.72)	0.300
Hesselink et al. 2004	LN	Improved adherence to treatment in patients under anti-inflammatory agents	24	30/58	17/40	1.22 (0.79 to 1.89)	0.380
Dierick-Van Daele et al. 2009	NP+	Adherence of clinicians to practical guidelines	0.5	143/179	96/126	1.05 (0.93 to 1.18)	0.450
Appropriate secondary prevention							
Campbell et al. 1998	NP	Aspirin management as secondary prevention: taken or contraindicated by allergy or peptic ulceration	12	466/575	373/562	1.22 (1.14 to 1.31)	<0.00001
Campbell et al. 1998	NP	Aspirin management as secondary prevention: taken or contraindicated by allergy or peptic ulceration	48	396/486	348/446	1.04 (0.98 to 1.11)	0.190
Campbell et al. 1998	NP	Low fat diet as appropriate secondary prevention	12	271/480	226/465	1.16 (1.03 to 1.31)	0.020
Campbell et al. 1998	NP	Low fat diet as appropriate secondary prevention	48	308/464	301/440	0.97 (0.89 to 1.06)	0.520
Campbell et al. 1998	NP	Moderate physical activity as appropriate secondary prevention: with an index of physical activity of >4	12	247/587	177/568	1.35 (1.16 to 1.58)	0.000
Campbell et al. 1998	NP	Moderate physical activity as appropriate secondary prevention: with an index of physical activity of >4	48	171/494	128/455	1.23 (1.02 to 1.49)	0.030
Campbell et al. 1998	NP	Non-smoking as appropriate secondary prevention	12	483/584	481/568	0.98 (0.93 to 1.03)	0.360
Campbell et al. 1998	NP	Non-smoking as appropriate secondary prevention	48	422/491	398/454	0.98 (0.93 to 1.03)	0.440
Hesselink et al. 2004	LN	Smoking cessation	24	4/45	6/38	0.56 (0.17 to 1.85)	0.340
Patient information and/or knowledge							
Chan et al. 2009	NP+	Provision of information on the causes of illness	6	78/78	12/40	3.26 (2.05 to 5.18)	<0.00001
Kinnersley et al. 2000	NP	Provision of information on the causes of illness	AC	501/619	491/682	1.12 (1.06 to 1.19)	<0.0001
Kinnersley et al. 2000	NP	Provision of information on the relief of symptoms	AC	548/637	467/687	1.27 (1.19 to 1.34)	<0.00001
Kinnersley et al. 2000	NP	Provision of information on the duration of illness	AC	404/631	388/681	1.12 (1.03 to 1.23)	0.009
Kinnersley et al. 2000	NP+	Provision of information on how to reduce the chance of recurrence	AC	205/603	139/662	1.62 (1.35 to 1.95)	<0.00001
Kinnersley et al. 2000	NP+	Provision of information on what to do if problems persist	AC	584/628	604/686	1.06 (1.02 to 1.09)	0.002
Shum et al. 2000	NP	Provision of information about self-medication	0.5–1	193/868	119/871	1.63 (1.32 to 2)	<0.00001
Shum et al. 2000	NP	Provision of information about general self-management	0.5–1	709/868	502/871	1.42 (1.33 to 1.51)	<0.00001
Chan et al. 2009	NP+	Provision of leaflets about patients' disease	6	78/78	5/40	7.41 (3.4 to 16.12)	<0.00001
Flynn et al. 1974	RN	Patients' knowledge of their special exercises	6–12	20/38	3/19	3.33 (1.13 to 9.83)	0.030

Flynn et al. 1974	RN	Patients' knowledge of complications of their disease	6–12	31/38	13/19	1.19 (0.85 to 1.68)	0.310
Lewis et al. 1967	LN	Patients' knowledge of their diagnosis, treatment, prescriptions, family involvement and other aspects of care	12		NR	NR	NR

Studies are listed in order of increasing length of follow-up, within each category of outcomes.
NP = nurse practitioner; NP+ = nurse practitioner with higher degree/course; RN = registered nurse; LN = licensed nurse; FUP = follow-up in months; n = number of patients with events; N = total number of patients per group; RR = relative risk; CI = confidence intervals; SBP = systolic blood pressure; DBP = diastolic blood pressure; DM2 = diabetes mellitus type 2; HbAc =, percent of glycosylated haemoglobin; mmol/l, millimoles per litre; mm Hg = millimetres of mercury; AC = after consultation.

This is not surprising. In many countries, until recently a person did not have to hold a Bachelor's degree in Nursing to be a nurse and nowadays nurses might have a masters or PhD degree. A nurse practitioner (NP) programme in the US for example requires a graduate degree [48]. In the UK, nurses working in NP roles were registered nurses who had undertaken a specific course of study to at least first degree (honours) level in 2008. By 2012, any nurses educationally prepared at bachelor's or master's level against the Royal College of Nursing competencies were entitled to be referred to as Advanced NPs [38]. This title requires a master's degree in Wales but not necessarily in the other three countries of the UK. Whether nurses' educational preparation or job titles (e.g. NP) with different educational degrees make a difference in the observed effects evaluated in this review cannot be concluded from the studies in question and should be examined further.

Accounts of responsibilities and tasks also varied across trials and were not described in sufficient detail. Due to the insufficient description of training content, we could not identify a common component across studies. In addition, it was generally assumed that nurses had the required competence to substitute physicians. However, the level of substitution (clinical autonomy) differed among trials and nurses seemed dependent of doctors' supervision in most studies. This may suggest the importance of collaborative models of care. Research has shown that team approaches in which nurses, physicians and other clinicians work collaboratively, might lead to better outcomes [49]. The implementation of inter-professional care management programmes should also be considered in future research.

The use of process guidelines or protocols to deliver the interventions was reported in nearly 75% of the studies which suggests that adherence to treatment, diet and provider guidelines can result in nurse care better or similar to

Table 5: Individual trial estimates from continuous data.

Reference details	Interventions, delivered by	Outcome reported	FUP, m	Nurse group, mean (SD)	Physician group, mean (SD)	SMD (95% CI)	p-value
Asthma							
Kuethe et al. 2011	NP+	Well controlled asthma based on Asthma Control Questionnaire: optimal and validated cut-off point of 0.75 (mean score of six items)	12	–0.22 (–0.49 to 0.05) *		†0.18 (–0.09 to 0.45)	‡ 0.57
Kuethe et al. 2011	NP+	Well controlled asthma based on Asthma Control Questionnaire: optimal and validated cut-off point of 0.75 (mean score of six items)	24	0.03 (–0.26 to 0.20) *		†–0.04(–0.19 to 0.27)	‡ 0.57
Visuomotor coordination							
Jarman et al. 2002	LN	Best hand score, health improvement	24	–45.3(21.2), N = 696	46(21.1), N = 558	–4.31 (–4.52 to –4.11)	<0.00001
BMI and Waist Circumference							
Voogdt-Pruis et al. 2010	NP+	Body Mass Index	12	27.2(1.17), N = 235	27.2(1.28), N = 281	0 (–0.21 to 0.21)	1.000
Houweling et al. 2011	NP	Body Mass Index	14	30.4(5.3), N = 102	30(4.5), N = 104	0.4 (–0.94 to 1.74)	0.560
Patient information and/or knowledge							
Dierick-Van Dale et al. 2009	NP+	Provision of information on the causes of problems or illness	AC	5.13(1.17), N = 688	5.21(1.16), N = 612	–0.08 (–0.21 to 0.05)	0.220
Dierick-Van Dale et al. 2009	NP+	Provision of information on the relief of symptoms	AC	5.33(1.04), N = 687	5.37(1.07), N = 614	–0.04 (–0.15 to 0.07)	0.500
Dierick-Van Dale et al. 2009	NP+	Provision of information on the duration of illness	AC	5.2(1.31), N = 683	5.28(1.41), N = 608	–0.08 (–0.23 to 0.07)	0.290
Dierick-Van Dale et al. 2009	NP+	Provision of information on how to reduce the chance of recurrence	AC	5.27(1.53), N = 685	5.42(1.62), N = 607	–0.15 (–0.32 to 0.02)	0.090
Dierick-Van Dale et al. 2009	NP+	Provision of information on what to do if problems persist	AC	5.36(1.24), N = 684	5.3(1.51), N = 610	0.06 (–0.09 to 0.21)	0.440
Lewis et al. 1967	LN	Patients' knowledge of their diagnosis, treatment, prescriptions, family involvement and other aspects of care	12	NR	NR	NR	NR

Studies are listed in order of increasing length of follow-up, within each category of outcomes.
NP = nurse practitioner; NP+ = nurse practitioner with higher degree/course; RN = registered nurse; LN = licensed nurse; FUP = follow-up in months; n = number of patients with events; N = total number of patients per group; SD = standard deviation; SMD = standard mean difference; CI = confidence intervals; AC = after consultation.
* Mean difference (90%CIs) for Nurses vs. General Physicians
† Mean difference (90%CIs) for Nurses vs. Paediatricians
‡ Nurses/General Physicians vs. Nurses/Paediatricians

that of physicians. In fact, the use of evidence-based clinical guidelines has shown effective improvement in the process and structure of care [50], and has been reported to aid the transfer of tasks between clinicians while maintaining and improving the quality of care [51]. The lack of reporting in adherence to guidelines or protocols in the other 25.6% of the studies may just be an indicator of the level of adherence and availability of guidelines in practice. These differences may result from the time and method of development, type of health problem, content of recommendations, and source of dissemination within others [52]. The finding that nurses are significantly more likely than physicians to provide life-style advice and information about various aspects of disease is consistent with previous reviews [9, 10], research reporting positive associations of nurse lifestyle interventions in the prevention of chronic disease [53] and reports showing patients' appreciation to nurses' involvement especially in education and counselling [54].

Despite all limitations, no study showed harm of nurse-led care interventions compared to physician-led care. Trained nurses seem to provide equal or better care compared to physicians for the management of chronic disease through process of care measures, within their scope of practice. We speculate that, regardless of the healthcare system in which nurses substitute physicians, and given the heterogeneity in patient populations, settings and interventions, the reasons for these effects may be that specific components of nurse training and competency are shared among studies (e.g. patient education). Another possibility is that nurses may adhere to process care guidelines and protocols better than physicians. In addition, individual trial estimates suggest that the effects of interventions may only be significant at short term (≤12 months), for some conditions such as asthma and COPD. These factors may have a significant impact on the continuity and quality of patient care and should be investigated in future studies.

Strengths and limitations of this systematic review

To our knowledge, this is the first systematic review of physician-nurse substitution with a focus on process of care outcomes. Our review updates earlier systematic reviews [9, 10] and uses a comprehensive search of the literature and critical appraisal of RCTs which are at lower risk of bias than other study designs [14, 55]. A particular strength of our review is that we examined individual trial data in relation to nurses' competencies and roles. It was however often difficult to understand in detail the role and responsibilities of nurses when substituting physicians. In many cases, nurses remain embedded in care teams that also involved physicians. It was also difficult to determine the nurses' level of education and whether the training competencies were appropriate for the type of care delivered. In many cases the description of training content is insufficient and limited the identification of common program components across studies. We excluded studies in which nurse-led teams were compared to physician-led care in a primary care base because of the potential confounding in the type of care/tasks (e.g. specialised vs. routine) and the type of clinician delivering the interventions. A limitation of the literature is the small number of studies that met the inclusion criteria. Although we did not search for grey literature and included publications in English only, we used thorough electronic and hand searches including the screening of relevant reviews (some in foreign languages). We did not contact study authors to further obtain or clarify missing information.

Conclusion

Our systematic review suggests that, in terms of process of care outcomes, special trained nurses can provide care that is at least as equivalent to care provided by physicians for chronic diseases such as diabetes, cardiovascular disorders, asthma, COPD, and hypertension. One limiting factor is the small number of studies reporting many unique processes of care measures. It is unclear whether the observed effects are due to the diversity in nurses' competencies, roles, and experiences. It is also unclear whether the components or contents of training competencies boost these effects. Future studies could benefit from the inclusion of larger samples, a more rigorous methodology, longer follow-up episodes, and mapping the wider range of nurse care from many countries. Consideration should be given to the role of multidisciplinary teams in which nurses embed their roles. Qualitative research could also add valuable information since it may allow the identification of factors that influence the performance and quality of care within the context of health care systems [56]. Future studies should especially provide precise accounts of the components of competencies or training programmes, and the qualifications, tasks and responsibilities of clinicians delivering substitution of care. In particular, the reporting of complex interventions according to recently proposed guidelines [57] may help establishing better reporting of substitution of care studies in the future. Consequently improving the interpretation of results and allowing the replication of interventions, so that future evaluations in decision-making can employ such evidence.

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of studies and on extraction of reported data. SD: contribution to the design and conceptualisation of the study; screening of titles, abstracts and full texts; acquisition of data and quality assessment. All authors read and approved the final version of the manuscript to be published.

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References

1 World Health Organization. The world health report: working together for health. Geneva, Switzerland: World Health Organization, 2006.

2 World Health Organization. Task shifting: rational redistribution of tasks among health workforce teams: global recommendations and guidelines. Geneva, Switzerland: World Health Organization, 2008.

3 World Health Organization. World Health Statistics 2012: Indicator compendium. Geneva, Switzerland: World Health Organization, 2012.

4 World Health Organization. Global Health Workforce Alliance: Reviewing Progress, Renewing Commitment. Progress Report on the Kampala Declaration and Agenda for Global Action. Geneva, Switzerland: World Health Organization, 2011.

5 Salsberg E, Grover A. Physician workforce shortages: implications and issues for academic health centers and policymakers. Acad Med. 2006;81:782–7.

6 Buchan J, O'May F. Determining skill mix in the health workforce: guidelines for managers and health professionals. Geneva, Switzerland: World Health Organization, 2000.

7 De Geest S, Moons P, Callens B, Gut C, Lindpaintner L, Spirig R. Introducing Advanced Practice Nurses / Nurse Practitioners in health care systems: a framework for reflection and analysis. Swiss Med Wkly. 2008;138:621–8.

8 Chopra M, Munro S, Lavis JN, Vist G, Bennett S. Effects of policy options for human resources for health: an analysis of systematic reviews. Lancet. 2008;371:668–74.

9 Horrocks S, Anderson E, Salisbury C. Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. BMJ. 2002;324:819–23.

10 Laurant M, Reeves D, Hermens R, Braspenning J, Grol R, Sibbald B. Substitution of doctors by nurses in primary care. Cochrane Database Syst Rev 2005:CD001271

11 Martinez-Gonzalez NA, Tandjung R, Djalali S, Huber-Geismann F, Markun S, Rosemann T. Effects of physician-nurse substitution on clinical parameters: a systematic review and meta-analysis. PLoS One 2014;9:e89181.

12 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.

13 Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054–60.

14 Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ. 2011;343:d5928.

15 Higgins JPT GS, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

16 Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ. 2002;325:652–4.

17 Review Manager (Revman) [Computer program]. Version 5.2.4. for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012 [http://www.cochrane.org/resources/handbook/].

18 Andryukhin A, Frolova E, Vaes B, Degryse J. The impact of a nurse-led care programme on events and physical and psychosocial parameters in patients with heart failure with preserved ejection fraction: a randomized clinical trial in primary care in Russia. Eur J Gen Pract. 2010;16(4):205–14.

19 Campbell NC, Ritchie LD, Thain J, Deans HG, Rawles JM, Squair JL. Secondary prevention in coronary heart disease: a randomized trial of nurse led clinics in primary care. Heart. 1998;80(5):447–52.

20 Campbell NC, Thain J, Deans HG, Ritchie LD, Rawles JM. Secondary prevention in coronary heart disease: baseline survey of provision in general practice. BMJ. 1998;316(7142):1430–4.

21 Campbell NC, Thain J, Deans HG, Ritchie LD, Rawles JM, Squair JL. Secondary prevention clinics for coronary heart disease: randomized trial of effect on health. BMJ. 1998;316(7142):1434–7.

22 Chan D, Harris S, Roderick P, Brown D, Patel P. A randomized controlled trial of structured nurse-led outpatient clinic follow-up for dyspeptic patients after direct access gastroscopy. BMC Gastroenterol. 2009;9:12.

23 Delaney EK, Murchie P, Lee AJ, Ritchie LD, Campbell NC. Secondary prevention clinics for coronary heart disease: a 10–year follow-up of a randomized controlled trial in primary care. Heart. 2008;94(11):1419–23.

24 Denver EA, Barnard M, Woolfson RG, Earle KA. Management of uncontrolled hypertension in a nurse-led clinic compared with conventional care for patients with type 2 diabetes. Diabetes Care. 2003;26(8):2256–60.

25 Dierick-Van Daele ATM, Metsemakers JFM, Derckx EWCC, Spreeuwenberg C, Vrijhoef HJM. Nurse practitioners substituting for general practitioners: Randomized controlled trial. J Adv Nurs. 2009;65(2):391–401.

26 Flynn BC. The effectiveness of nurse clinicians' service delivery. Am J Public Health. 1974;64(6):604–11.

27 Hesselink AE, Penninx BW, van der Windt DA, van Duin BJ, de Vries P, Twisk JW, et al. Effectiveness of an education programme by a general practice assistant for asthma and COPD patients: results from a randomized controlled trial. Patient Educ Couns. 2004;55(1):121–8.

28 Houweling ST, Kleefstra N, van Hateren KJJ, Groenier KH, Meyboom-de Jong B, Bilo HJG. Can diabetes management be safely transferred to practice nurses in a primary care setting? A randomized controlled trial. J Clin Nurs. 2011;20(9/10):1264–72.

29 Jarman B, Hurwitz B, Cook A, Bajekal M, Lee A. Effects of community based nurses specialising in Parkinson's disease on health outcome and costs: randomized controlled trial. BMJ. 2002;324(7345):1072–5.

30 Kinnersley P, Anderson E, Parry K, Clement J, Archard L, Turton P, et al. Randomised controlled trial of nurse practitioner versus general practitioner care for patients requesting "same day" consultations in primary care. BMJ. 2000;320(7241):1043–8.

31 Kuethe M, Vaessen-Verberne A, Mulder P, Bindels P, van Aalderen W. Paediatric asthma outpatient care by asthma nurse, paediatrician or general practitioner: Randomised controlled trial with two-year follow-up. Primary Care Respiratory Journal. 2011;20(1):84–91.

32 Lewis CE, Resnik BA. Nurse clinics and progressive ambulatory patient care. N Engl J Med. 1967;277(23):1236–41.

33 Murchie P, Campbell NC, Ritchie LD, Deans HG, Thain J. Effects of secondary prevention clinics on health status in patients with coronary heart disease: 4 year follow-up of a randomized trial in primary care. Fam Pract. 2004;21(5):567–74.

34 Murchie P, Campbell NC, Ritchie LD, Simpson JA, Thain J. Secondary prevention clinics for coronary heart disease: four year follow up of a randomized controlled trial in primary care. BMJ. 2003;326(7380):84.

35 Raftery JP, Yao GL, Murchie P, Campbell NC, Ritchie LD. Cost effectiveness of nurse led secondary prevention clinics for coronary heart disease in primary care: follow up of a randomized controlled trial. BMJ. 2005;330(7493):707.

36 Shum C, Humphreys A, Wheeler D, Cochrane MA, Skoda S, Clement S. Nurse management of patients with minor illnesses in general practice: multicentre, randomized controlled trial. BMJ. 2000;320(7241):1038–43.

37 Voogdt-Pruis HR, Beusmans GHMI, Gorgels APM, Kester ADM, Van Ree JW. Effectiveness of nurse-delivered cardiovascular risk management in primary care: A randomized trial. Br J Gen Pract. 2010;60(570):40–6.

38 Royal College of Nursing. Advanced Nurse Practitioners – an RCN Guide to the Advanced Nurse Practitioner Role, Competences and Programme Accreditation. In London: RCN; 2012.

39 Cooper R, Stoflet S. Diversity and consistency: the challenge of maintaining quality in a multidisciplinary workforce. J Health Serv Res Policy. 2004;9(Suppl 1):39–47.

40 Association of American Medical Colleges. Physician Shortages to Worsen Without Increases in Residency Training; 2011.

41 Cooper RA, Laud P, Dietrich CL. Current and projected workforce of non-physician clinicians. JAMA. 1998;280(9):788–94.

42 Delamaire M, Lafortune G. Nurses in Advanced Roles: A Description and Evaluation of Experiences in 12 Developed Countries, OECD Health Working Papers, 2010;No. 54, OECD Publishing. Available from http://dx.doi.org/10.1787/5kmbrcfms5g7–en

43 Aiken LH, Sloane DM, Bruyneel L, Van den Heede K, Griffiths P, Busse R, et al. Nurse staffing and education and hospital mortality in nine European countries: a retrospective observational study. Lancet. 2014, Feb 25. DOI: 10.1016/S0140–6736(13)62631–8.

44 Blegen MA, Goode CJ, Park SH, Vaughn T, Spetz J. Baccalaureate education in nursing and patient outcomes. J Nurs Adm. 2013;43:89–94.

45 Friese CR, Lake ET, Aiken LH, Silber JH, Sochalski J. Hospital nurse practice environments and outcomes for surgical oncology patients. Health Serv Res. 2008;43:1145–63.

46 Kutney-Lee A, Sloane DM, Aiken LH. An increase in the number of nurses with baccalaureate degrees is linked to lower rates of postsurgery mortality. Health Aff. (Millwood) 2013;32:579–86.

47 Tourangeau AE, Doran DM, McGillis Hall L, O'Brien Pallas L, Pringle D, Tu JV, Cranley LA. Impact of hospital nursing care on 30-day mortality for acute medical patients. J Adv Nurs. 2007;57:32–44.

48 Morgan S. What are the differences in nurse practitioner training and scope of practice in the US and UK? Nurs Times. 2010;106:21–4.

49 Leventhal ME, Denhaerynck K, Brunner-La Rocca HP, Burnand B, Conca-Zeller A, Bernasconi AT, et al. Swiss Interdisciplinary Management Programme for Heart Failure (SWIM-HF): a randomised controlled trial study of an outpatient inter-professional management programme for heart failure patients in Switzerland. Swiss Med Wkly. 2011;141:w13171.

50 Lugtenberg M, Burgers JS, Westert GP. Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. Quality & safety in health care. 2009;18(5):385–92.

51 Thomas L, Cullum N, McColl E, Rousseau N, Soutter J, Steen N. Guidelines in professions allied to medicine. Cochrane Database Syst Rev. 2000(2):Cd000349.

52 Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ. 1997,157(4):408–16.

53 Sargent GM, Forrest LE, Parker RM. Nurse delivered lifestyle interventions in primary health care to treat chronic disease risk factors associated with obesity: a systematic review. Obes Rev. 2012;13(12):1148–71.

54 Rosemann T, Joest K, Korner T, Schaefert R, Heiderhoff M, Szecsenyi J. How can the practice nurse be more involved in the care of the chronically ill? The perspectives of GPs, patients and practice nurses. BMC Fam Pract. 2006;7:14.

55 Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomized intervention studies. Health technology assessment (Winchester, England). 2003;7(27):iii-x, 1–173.

56 Hoff TJ, Witt LC. Exploring the use of qualitative methods in published health services and management research. Med Care Res Rev. 2000;57(2):139–60.

57 Möhler R, Bartoszek G, Meyer G. Quality of reporting of complex healthcare interventions and applicability of the CReDECI list – a survey of publications indexed in PubMed. BMC Med Res Methodol. 2013;13(1):1–8.

Annex: Supplementary data.

Table S1: PRISMA Checklist.

Table S2: Search strategy in Ovid Medline.
Similar search strategies were performed and run in EMBASE, The Cochrane Library of Systematic Reviews and CINAHL and include specific search filters for RCTs.

Table S3: Studies excluded with reasons for exclusion based on appraisal of full text articles.

Table S4: Characteristics of participants, interventions and outcomes in the studies included in review.

Table S1: PRISMA Checklist. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2 and Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2, 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2, 3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2, 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3, table 1, table 2, table S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4, table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4–7, table 4, table 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4, Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7–11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

Table S2: Search strategy in Ovid Medline*

Item, #	Searches	Results
1	exp General Practice/ or exp Primary Health Care/ or exp Private Practice/ or Family Physicians/ or general practitioners/ or physicians, primary care/ or exp geriatrics/ or Geriatric Assessment/ or exp pediatrics/	235,871
2	exp Nursing Care/ or Primary Nursing/ or Community Health Nursing/ or Family Nursing/ or Nursing, Practical/ or Advanced Practice Nursing/ or exp Geriatric Nursing/ or exp Pediatric Nursing/	132,684
3	exp Ambulatory Care/ or ambulatory care facilities/ or community health centers/ or maternal-child health centers/ or outpatient clinics, hospital/ or pain clinics/ or surgicenters/	78,635
4	(primary adj2 (health?care$ or care$ or medic$)).ti,ab,hw.	106,920
5	((family adj2 (physician$ or doctor or practitioner or practice or internist or medic$)) or (general adj2 (internist or physician$ or doctor or practitioner or practice or medic$ or care$ or health$care$)) or (personal adj2 (doctor or physician$)) or (physician$ adj2 (practitioner or practice)) or (internal adj medicine) or geriatri$ or paediatri$ or pediatri$).ti,ab,hw,mp.	500,300
6	((community or ambulatory or shared) adj4 (care$ or health$care) adj4 (facility or facilities or service$ or cent$ or clinic$)).ti,ab,hw.	16,580
7	or/1-6	769,622
8	exp Physician Assistants/ or nurse clinicians/ or nurse practitioners/	24,593
9	(nurs$ adj2 (family or primary or care$ or practitioner or practice or clinic$ or regist$ or specialist$ or leader or consultant$ or physician$ or expert or district or advanced or assessment or visit$ or geriatri$ or paediatri$ or pediatri$)).tw,mp.	158,263
10	((nurs$ adj2 appropriately adj trained) or (nurs$ adj2 community adj2 health adj2 care) or (nurs$ adj2 first contact) or (assistan$ adj2 (physician$ or medic$ or health$care$)) or (clinic$ adj2 support) or (clinic$ adj2 (nurse$led or nurse led))).ti,ab,hw.	22,441
11	or/8-10	185,383
12	Nurse's Practice Patterns/	859
13	delegation, professional/	397
14	professional autonomy/	8,318
15	Clinical Competence/	63,230
16	exp Professional Role/	64,848
17	12 or 13 or 14 or 15 or 16	128,,584
18	(((substitut$ or transfer$ or swap or replac$) adj3 (((doctor$ or GP or GPs or physician$ or practi$ or general) adj2 practitioner$) or job or role or task$ or skill$ or perform$ or responsibility or autonom$)) or ((delegat$ or supervis$) adj5 (responsibility or performance$ or role$ or job or tasks)) or (autonom$ adj (professional or responsibility or self$regulation)) or (clinical adj skill$ adj competence) or (((skill$mix or skill$) adj mix$) or skill$) or (role$ adj4 (advance or chang$ or enhanc$ or expan$ or transfer$)) or (team$ adj4 (patient care or multidisciplinary or cooperation) adj4 autonom$)).ti,ab,hw.	166,854
19	17 or 18	277,555
20	7 and 11 and 19	15,643
21	(letter or letter$).pt,sh. or (editorial or historical article or anecdote or commentary or note or case report$ or case study).pt. or (editorial or historical article or anecdote or commentary or note or case report$ or case study).pt. or (animal studies or animals, laboratory or experimental animal or animal experiment or animal model or rodentia or rodents or rodent).sh.	2,968,746
22	(randomi?ed controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo or randomly or trial or groups).ab.	1,926,021
23	exp cluster analysis/ or cross-over studies/ or ((cluster$ adj2 random$) or (communit$ adj2 intervention$) or (communit$ adj2 random$)).mp.	83,918
24	((non$equivalent adj3 control$) or posttest$ or post test$ or post-test$ or pre test$ or pretest$ or pre-test$ or quasi-experiment$ or quasi experiment$ or quasiexperiment$ or timeseries or time series or time-series or (time adj2series adj2 analysis) or (interrupted adj2 time adj2series)).mp.	40,132
25	22 or 23 or 24	1,993,858
26	25 not 21	1,965,071
27	20 and 26	1,511
28	limit 27 to humans (updated by mid-February 2014)	1,459
* Similar search strategies were performed and run in EMBASE, The Cochrane Library of Systematic Reviews and CINHAL and include specific search filters for RCTs.		

Table S3: Studies excluded with reasons for exclusion based on appraisal of full text articles.

Ref. #	Reference to study	Reason for exclusion
1	Dierick-Van Daele ATM, Steuten LMG, Metsemakers JFM, Derckx EWCC, Spreeuwenberg C, Vrijhoef HJM. Economic evaluation of nurse practitioners versus GPs in treating common conditions. British Journal of General Practice. 2010;60:28-33.	Outcomes of interest not reported.
2	Du Moulin MFMT, Hamers JPH, Paulus A, Berendsen CL, Halfens R. Effects of introducing a specialized nurse in the care of community-dwelling women suffering from urinary incontinence: a randomized controlled trial. J Wound Ostomy Continence Nurs. 2007;34:631-40.	Outcomes of interest not reported.
3	Fairall L, Bachmann MO, Lombard C, Timmerman V, Uebel K, Zwarenstein M, et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. The Lancet. 2012.	Outcomes of interest not reported.
4	Hemani A, Rastegar DA, Hill C, al-Ibrahim MS. A comparison of resource utilization in nurse practitioners and physicians. Eff Clin Pract. 1999;2:258-65.	Outcomes of interest not reported.
5	Hiss RG, Armbruster BA, Gillard ML, McClure LA. Nurse care manager collaboration with community-based physicians providing diabetes care: a randomized controlled trial. Diabetes Educator. 2007;33:493-502.	Outcomes of interest not reported.
6	Hollinghurst S, Horrocks S, Anderson E, Salisbury C. Comparing the cost of nurse practitioners and GPs in primary care: modelling economic data from randomised trials. British Journal of General Practice. 2006;56:530-5.	Outcomes of interest not reported.
7	Kernick D, Cox A, Powell R, Reinhold D, Sawkins J, Warin A. A cost consequence study of the impact of a dermatology-trained practice nurse on the quality of life of primary care patients with eczema and psoriasis. British Journal of General Practice. 2000;50:555-8.	Outcomes of interest not reported.
8	Kernick D, Powell R, Reinhold D. A pragmatic randomised controlled trial of an asthma nurse in general practice. Primary Care Respiratory Journal. 2002;11:6-8.	Outcomes of interest not reported.
9	Lenz ER, Mundinger MO, Kane RL, Hopkins SC, Lin SX. Primary care outcomes in patients treated by nurse practitioners or physicians: two-year follow-up. Med Care Res Rev. 2004;61:332-51.	Outcomes of interest not reported.
10	Mundinger MO, Kane RL, Lenz ER, Totten AM, Tsai WY, Cleary PD, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. Jama. 2000;283:59-68.	Outcomes of interest not reported.
11	Venning P, Durie A, Roland M, Roberts C, Leese B. Randomised controlled trial comparing cost effectiveness of general practitioners and nurse practitioners in primary care. BMJ. 2000;320:1048-53.	Outcomes of interest not reported.
12	Winter C. Quality health care: patient assessment [MSc]. Long Beach, CA: California State University; 1981.	Outcomes of interest not reported.
13	Blanchard MR, Waterreus A, Mann AH. The effect of primary care nurse intervention upon older people screened as depressed. Int J Geriatr Psychiatry. 1995;10:289-98.	Cohort study and multidisciplinary team approach.
14	Blanchard MR, Waterreus A, Mann AH. Can a brief intervention have a longer-term benefit? The case of the research nurse and depressed older people in the community. Int J Geriatr Psychiatry. 1999;14:733-8.	Nurse working in close collaboration with other clinicians.
15	Cave AJ, Wright A, Dorrett J, McErlain M. Evaluation of a nurse-run asthma clinic in general practice. Primary Care Respiratory Journal. 2001;10:65-8.	Not an intervention comparison between nurses and physicians.
16	Krein SL, Klamerus ML, Vijan S, Lee JL, Fitzgerald JT, Pawlow A, et al. Case management for patients with poorly controlled diabetes: a randomized trial. Am J Med. 2004;116:732-9.	Nurse working in close collaboration with other clinicians based on a chronic care model.
17	Lapointe F, Lepage S, Larrivee L, Maheux P. Surveillance and treatment of dyslipidemia in the post-infarct patient: can a nurse-led management approach make a difference? Can J Cardiol. 2006;22:761-7.	Intervention (telephone) not of interest for this review and not part of usual care interventions of physicians.
18	Leenders F, Beusmans G, Swerts H, editors. A practice nurse for patients with cardiovascular disease, an explorative study 2006.	Report in Dutch. Version of article in English was not found.
19	Lewis CE, Resnik BA, Schmidt G, Waxman D. Activities, events and outcomes in ambulatory patient care. N Engl J Med. 1969;280:645-9.	Not at RCT.
20	Sackett DL, Spitzer WO, Gent M, Roberts RS. The Burlington randomized trial of the nurse practitioner: health outcomes of patients. Ann Intern Med. 1974;80:137-42.	No real substitution. At least 30% of patients in both groups were seen by the physicians at the end of study and data not split into mutually exclusive groups.
21	Spitzer WO, Sackett DL, Sibley JC, Roberts RS, Gent M, Kergin DJ, et al. The Burlington randomized trial of the nurse practitioner. N Engl J Med. 1974;290:251-6.	No real substitution. At least 30% of patients in both groups were seen by the physicians at the end of study and data not split into mutually exclusive groups.
22	Tonstad S, Alm CS, Sandvik E. Effect of nurse counselling on metabolic risk factors in patients with mild hypertension: a randomised controlled trial. Eur J Cardiovasc Nurs. 2007;6:160-4.	No real substitution. In both experimental and control groups the nurse provides interventions at different stages of care.
23	Van Son L, Vrijhoef, H. Supporting the general practitioner. A randomized controlled trial investigation the effects of a practice nurse on asthma, COPD, and diabetes. 2004; Huisarts en wetenschap:15-21.	Report in Dutch. Version of article in English was not found.
24	Williams KS, Assassa RP, Cooper NJ, Turner DA, Shaw C, Abrams KR, et al. Clinical and cost-effectiveness of a new nurse-led continence service: a randomised controlled trial. Br J Gen Pract. 2005;55:696-703.	Nurse working in close collaboration with other clinicians. Control group received care from nurses, physicians and specialists and data not split into mutually exclusive groups.

Table S4: Characteristics of participants, interventions and outcomes, in the studies included in review.

Study			Participants		Intervention			Outcomes
First author, year	**Location**	**Design, period***	**Included**	**Excluded**	**Care delivered**	**Clinical autonomy**	**Follow-up, months**	**Reported**
Houweling et al. 2011	NL 5	RCT, period NR.	Patients under treatment and under medication for diabetes mellitus type 2, with HbA1c measurements within the last three years.	Patients with diabetes mellitus type 2 not being treated in primary care setting, inability to participate because of age, comorbidities or -in the opinion of the general practitioner- whoever was not willing to return for follow-up.	Practice nurse with one week training in diabetes mellitus to manage transferred patients based on guidelines.	Full responsibility.	14	BP, TC, GH, TC/HDL ratio.
Kuethe et al. 2011	NL 4	RCT, 2006–2008.	Patients 6–16 years old with moderate and stable asthma, in treatment of inhalative corticosteroids at least nine months before the start of the study, informed consent.	Patients not able to perform lung function tests, or who had other chronic diseases.	Asthma nurse to manage patients based on guidelines.	Nurses needed support from/or short communication with paediatrician.	24	Lung function: PD20, %FEV1, FENO.
Voogdt-Pruis et al. 2010	NL 3	RCT, 2006–2007.	Patients 30–74 years of age, with cardiovascular disease or hypertension and/or hypercholesterolemia, with at least 10% in 10-year risk of cardiovascular disease; risk due to systolic blood pressure of ≥140 or total cholesterol of ≥6.5 mmol/l within the previous six months.	Patients visiting specialist in cardiovascular disease more than once per year, diabetes mellitus, severe comorbidities.	Nurse-led care based on Dutch guidelines for cardiovascular risk management. Advance practice nurse managed cardiovascular risk including primary and secondary prevention.	NR.	12	BP, TC.
Andryukhin et al. 2010	RU 1	RCT, 2006–2009.	Patients of at least 50 years of age with Heart Failure with preserved ejection fraction, informed consent.	Patients with blood pressure of <90/60 mm Hg or >160/100 mm Hg, under optimal antihypertensive therapy, acute coronary syndrome within previous six months, significant valvular stenosis, insulin diabetes mellitus dependent, confirmed chronic obstructive pulmonary disease, conditions limiting participation in the rehabilitation (see reference for more details).	Nurse-led care based on Russian National guidelines. Nurses with special degree in patient education obtained in joint course: patient education, treatment and exercise training information and counselling.	Prescription of medication and non-pharmacological measures (diet, alcohol intake, weight reduction, smoking cessation, activity and exercise training) provided by physician.	6	TC, GH, LDL, cardiac function and inflammation.
Dierick-Van Daele et al. 2009	NL 2	RCT, 2006.	Patients with common complaints aged ≥16 who sought physician for initial consultation	Patients unregistered in practice, language or reading problems, or with reason for appointment not provided.	Nurse practitioner with Master degree in AN, trained in common complaints to manage patients based on GDLs (assess symptoms, perform PE and diagnosis; decisions on further treatment, prescribing, referrals to 1ry and 2ry services, ordering clinical tests and investigations)	Prescriptions and referrals had to be validated by physician.	0.5, AC	Adherence to practical guidelines, provision of information about causes and duration of disease, symptoms relief, recurrences minimisation and how to deal with persistent issues.

Chan et al. 2009	UK 6	RCT, 2002–2004.	Patients with mild gastro-oesophageal reflux disease or moderate gastritis referred to gastroscopy for evaluation	Patients with sinister symptoms (dysphagia, vomiting, anaemia, rapid weight loss, history of gastric surgery, severe gastroscopic findings e.g. peptic ulcer, tumour, esophagitis grade C/D, Barrett's oesophagus	Gastrointestinal nurse practitioner to manage Dyspepsia based on GDLs and to run follow to up clinic for consultations following gastroscopy.	Authorised to adopt treatment according to GDLs and perform specific tests (e.g. breath urea, barium meal).	6	Provision of information on cause of illness and provision of leaflets about the disease.
Hesselink et al. 2004	NL 1	RCT, 1998–2002.	Patients with asthma, COPD or mixed disease aged 16 to 75 years, with symptoms (cough, phlegm or dyspnoea) within year before study, with current use of COPD or asthma medication	Patients with presence of other pulmonic disease, terminal disease	Physician's assistants to manage patients based on semi-structured protocols: Asthma and COPD patient education	No (details NR).	24, 12	Correct inhalation technique, treatment adherence and smoking cessation.
Denver et al. 2003	UK 5	RCT, 2000–2001.	Patients with diabetes mellitus type 2, previous diagnosis of hypertension, or who were in receipt of blood pressure lowering treatment.	Patients with life-threatening comorbidities requiring intensive management.	Hypertension nurse care based on clinical guidelines.	No (details NR).	6	BP, TC, HG, HDL, triglycerides, kidney function.
Jarman et al. 2002	UK 4	RCT, 1996–1999.	Patients with Parkinson's disease taking one or more anti-Parkinson drugs, informed consent.	Patients younger than17 years of age, severe mental illness, sufficient cognitive impairment.	Community nurse with a course in Parkinson's disease: advised physicians, provided patient counselling and education, treatment information and monitoring; reporting to physicians, instigating respite, day hospital care and discharge; assessment of patient social security, liaison with multidisciplinary primary care teams for ongoing assessment and therapy.	Nurses were under guidance of a nurse manager but had advisory position to physicians with whom patients' records were discussed.	24	Stand-up and mobility (tests).
Kinnersley et al. 2000	UK 3	RCT, period NR.	Patients with diverse complaints requesting same day appointments, informed consent	Patients seemingly too ill to wait or unable to understand the research, women seeking emergency contraception	Nurse practitioner with a nurse diploma on care for same day consultations for primary care	Physicians were always available to prescribe when necessary.	AC	Provision of information about causes and duration of disease, symptoms relief, recurrences minimisation and how to deal with persistent issues.
Shum et al. 2000	UK 2	RCT, 1998–1999.	Patients with minor illnesses aged ≥1 years, who requested and were given appointment on the same day, informed consent	Patients with pregnancy problems, severe chest or abdominal pain, severe breathing problems, vomiting blood, fits or blackouts, psychiatric problems, literacy or language difficulties	Nurse practitioner who had no specific experience in seeing patients with minor illnesses but took a course on managing minor illnesses and were piloted before the study: management, history taking, physical examinations, advice and treatment, prescribing and referral	Prescriptions required a doctor's signature.	0.5–1	Provision of information about self-medication and general self-management.

Campbell et al. 1998	UK 1	RCT, 1995–1996.	Patients with CHD	Patients with terminal illness, dementia, housebound patient, explicit request to see physician.	Health visitors, district and practice nurses with training in clinic protocols/GDLs and techniques to facilitate behavioural change: secondary prevention of CHD.	No full responsibility to manage patients.	12, 48	BP and lipids managed according to GDLs, appropriate secondary prevention through aspirin management, low-fat diet, physical activity and non-smoking.
Flynn et al. 1974	US 2	RCT, 1971.	Patients with undifferentiated conditions with informed consent were referred to nurse clinician	NR	Nurse clinicians with training in service delivery including health status, quantity and efficiency of care.	Nurses were authorised to order medication and tests.	6–12	Adherence to treatment and diet and patients' knowledge of their complications of disease and on their exercises prescribed.
Lewis et al. 1967	US 1	RCT, period NR.	Patients with HBP, CVD, obesity, somatisation problems, rheumatoid or degenerative arthritis	NR	Nurses who provided primary source care for at least 1 year before the study to provide care based on GDLs: routine management, schedule appointments and care following standing orders written for patients in each diagnostic class.	The diagnostic class defined the limits for nurses autonomy i.e. initiation or alteration of care; patient charts seen by nurse were reviewed daily by 1–2 physicians involved in the project.	12	Patients' knowledge of their diagnosis, treatment, prescriptions, family involvement or other aspects of care.

Studies are listed by year (y) of publication, in decreasing order.
US = United States; NL = The Netherlands; UK = United Kingdom; ZA = South Africa; RU = Russia; RCT = randomised controlled trial; cRCT = cluster randomised controlled trial; NR = not reported; ART = antiretroviral therapy; HbA1c = haemoglobin; BP = blood pressure; TC = total cholesterol; GH = glycosylated haemoglobin; CD4 = T-cell surface glycoprotein CD4; HDL = high density lipoprotein levels; LDL = low density lipoprotein; PD20 = provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV1); FENO = fraction of exhaled nitric oxide; AC = after consultation.
* start and end year when studies were conducted.

Figures (large format)

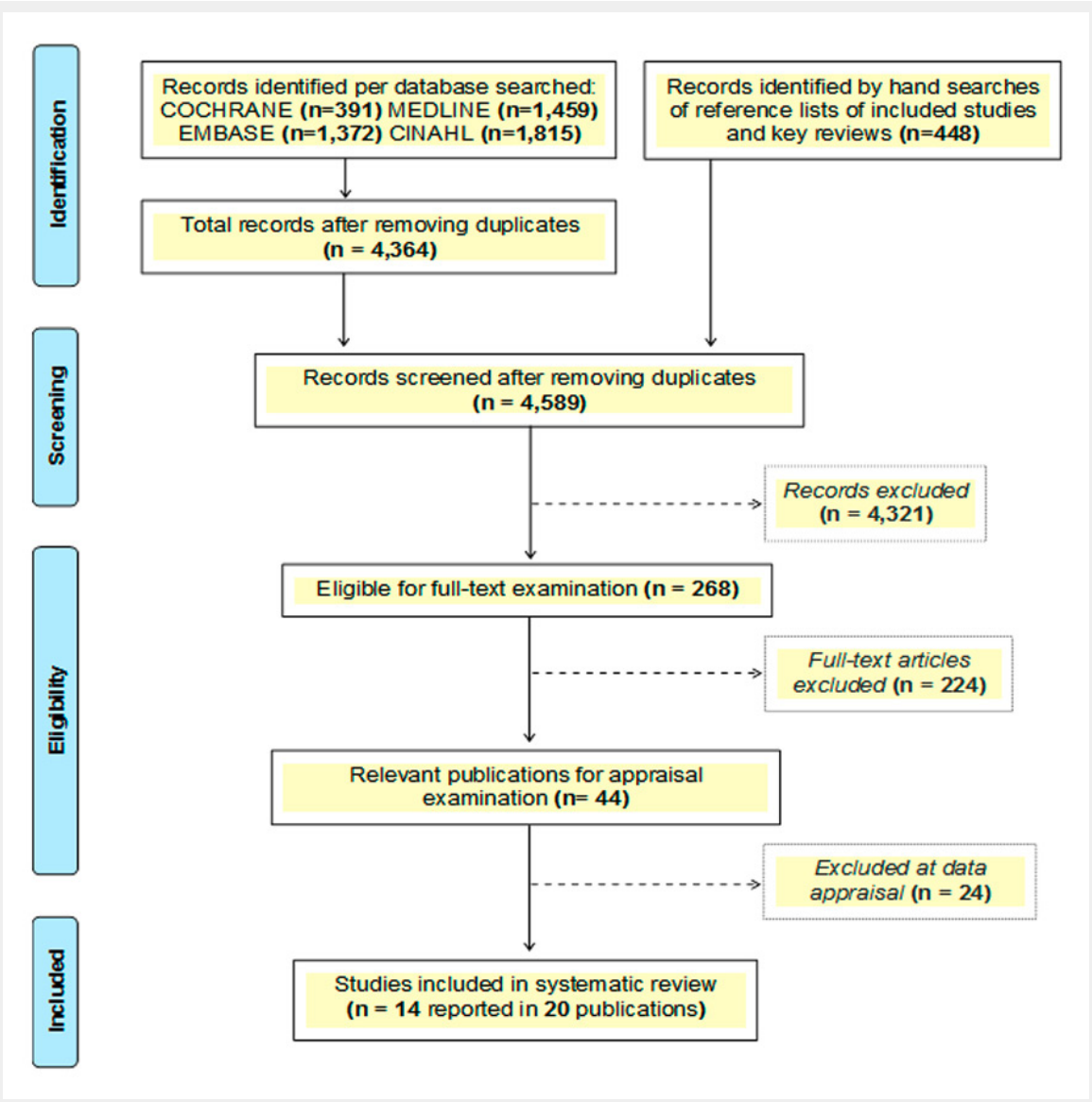

Figure 1

Flow diagram – study selection process.