

RESEARCH ARTICLE

Open Access

Substitution of physicians by nurses in primary care: a systematic review and meta-analysis

Nahara Anani Martínez-González¹, Sima Djalali¹, Ryan Tandjung¹, Flore Huber-Geismann¹, Stefan Markun¹, Michel Wensing^{1,2} and Thomas Rosemann^{1*}

Abstract

Background: In many countries, substitution of physicians by nurses has become common due to the shortage of physicians and the need for high-quality, affordable care, especially for chronic and multi-morbid patients. We examined the evidence on the clinical effectiveness and care costs of physician-nurse substitution in primary care.

Methods: We systematically searched OVID Medline and Embase, The Cochrane Library and CINAHL, up to August 2012; selected and critically appraised published randomised controlled trials (RCTs) that compared nurse-led care with care by primary care physicians on patient satisfaction, Quality of Life (QoL), hospital admission, mortality and costs of healthcare. We assessed the individual study risk of bias, calculated the study-specific and pooled relative risks (RR) or standardised mean differences (SMD); and performed fixed-effects meta-analyses.

Results: 24 RCTs (38,974 participants) and 2 economic studies met the inclusion criteria. Pooled analyses showed higher overall scores of patient satisfaction with nurse-led care (SMD 0.18, 95% CI 0.13 to 0.23), in RCTs of single contact or urgent care, short (less than 6 months) follow-up episodes and in small trials ($N \le 200$). Nurse-led care was effective at reducing the overall risk of hospital admission (RR 0.76, 95% CI 0.64 to 0.91), mortality (RR 0.89, 95% CI 0.84 to 0.96), in RCTs of on-going or non-urgent care, longer (at least 12 months) follow-up episodes and in larger (N > 200) RCTs. Higher quality RCTs (with better allocation concealment and less attrition) showed higher rates of hospital admissions and mortality with nurse-led care albeit less or not significant. The results seemed more consistent across nurse practitioners than with registered or licensed nurses. The effects of nurse-led care on QoL and costs were difficult to interpret due to heterogeneous outcome reporting, valuation of resources and the small number of studies.

Conclusions: The available evidence continues to be limited by the quality of the research considered. Nurse-led care seems to have a positive effect on patient satisfaction, hospital admission and mortality. This important finding should be confirmed and the determinants of this effect should be assessed in further, larger and more methodically rigorous research.

Keywords: Systematic review, Meta-analysis, Physician-nurse substitution, Skill-mix, Health outcomes, Cost

Background

Concerns about the global shortage of health care providers [1,2] continue to fuel the debate about the need to introduce new strategies of health care delivery. Especially, the increasing shortage of physicians makes substitution by nurses a common demand which is expected to escalate with ageing populations and an increasing prevalence of chronic conditions. Two systematic reviews published ten years ago suggested that care provided by nurses might be equally good as the care provided by physicians [3,4]. Health outcomes, use of resources and healthcare costs were found to be similar between nurses and physicians while patient satisfaction was similar or better with nurse-led care. These differences, however, were limited by the low volume and quality of the studies. In this context, it is also important to consider that nurses' education continues to evolve resulting in different roles and qualifications across different health care systems. It seems



© 2014 Martínez-González et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

^{*} Correspondence: Thomas.Rosemann@usz.ch

¹Institute of Primary Care, University Hospital Zurich, Pestalozzistrasse 24, 8091 Zurich, Switzerland

Full list of author information is available at the end of the article

timely therefore to assess whether the updated evidence would support the notion that nurses can substitute physicians in specific clinical tasks. Therefore, we performed a systematic review and meta-analysis of trials investigating the clinical effectiveness and costs of nurses working as substitutes for physicians in primary care.

Methods

We followed a protocol developed prior to starting the review and followed the PRISMA guidelines [5] for the reporting of systematic reviews and meta-analyses (Additional file 1: Table S1).

Study inclusion/exclusion criteria

We included peer reviewed randomised controlled trials (RCTs) from any country published in English in which nurses (in any type of role) substituted physicians by acting as the main figure of care with autonomous or delegated clinical responsibility for tasks that would have formerly been performed by physicians alone: where nurse-led care was compared to physician-led care (family physicians, paediatricians, and geriatricians); the intervention had taken place in general practices, community or ambulatory care settings; in patients of all ages seeking care for all conditions including mental health and addiction restricted to primary care; and which reported on patient satisfaction, quality of life (QoL), hospital admission, mortality and cost of health services. Following the framework published in a Cochrane review [3], we excluded studies in which nurses firstly, provided services which supplemented or extended the care provided by physicians or tasks that are not part of the usual care of physicians and secondly, where nurses collaborated with other clinicians in a team and thus the effect of nurse-led care, as the main intervention, could not be distinguished.

Study identification

We searched OVID Medline, Embase, CINAHL and The Cochrane Library of Systematic Reviews which includes the Cochrane Effective Practice and Organisation of Care Group, from all available dates until August 2012. The searches, not age-, date- or country-specific included 'primary care', 'skill-mix', 'physicians'-'nurse' substitution' (Additional file 1: Table S2). We also manually searched the reference lists of included studies and relevant reviews.

Assessment of study quality

We assessed the risk of bias of all trials without the calculation of a composite score following available guidelines [6-8]. We considered bias due to attrition of more than 20% to be of significant concern; and adequate intentionto-treat (ITT) if trial authors analysed participants based on their original group allocation regardless of protocol violations or non-compliance [9].

Data extraction

Both qualitative (characteristics of studies, population and interventions) and numeric data (dichotomous and continuous format) were extracted using structured data collection forms, designed and pilot-tested *a-priori*. If more than one comparison group of interest were reported, these were combined and compared as one to nurse-led care. If the results from a single study were reported in more than one publication, data were extracted as one study. When one publication reported more than one cohort, data were extracted as separate studies.

Selection and assessment of studies and acquisition of data

Two authors independently screened titles and abstracts, assessed both the full-text of eligible publications and the risk of bias of included studies, and extracted data. Differences were resolved through consensus.

Statistical analyses

We calculated the individual and pooled unadjusted relative risks (RR) and the standardised mean differences (SMD); and performed meta-analyses when at least three trials reported appropriate data, using the inverse variance fixed-effects (FE) method and repeated the analyses using a random-effects (RE) model in Cochrane RevMan (Version 5.1) [10]. We report the summary statistics, their 95% confidence intervals (CI) and consider p < 0.05statistically significant. When scales pointed in opposite directions, we subtracted the mean from the maximum possible value of the scale and estimated the standard deviations (SD) using well-established techniques [11]. We analysed dichotomous and continuous data together by converting ORs to an effect size expressed in SMD using available methods [12]. We decided to use a FE model in keeping with: 1) having no basis to assume that the effects had a normal distribution, 2) the small number of studies in at least two of the analyses, 3) the accuracy in estimates and CIs that FE provides even in a small number of studies and the more weight assigned to larger studies; RE gives similar weight to small and larger studies. We quantified heterogeneity using the I^2 statistic [13] and explored the effects of nurse-led care and potential sources of I² by pooling data into pre-specified subgroup analyses by clinical characteristics: nurses' roles (based on reported details: nurse practitioner with higher degree courses/specialisation (NP+) versus nurse practitioner (NP) versus registered/licensed nurse (RN/LN), type of care (single contact versus on-going care; urgent versus non-urgent) and length of follow-up (months: <6 versus ≥ 6 ; <12 versus ≥ 12). We explored the effect of potential sources of bias by study size (small, N < 200 versus

large, N \geq 200), allocation concealment (adequate *versus* inadequate/unclear) and attrition (<20% *versus* \geq 20%), and inspected publication bias using funnel plots where there were at least 10 trials [14]. We performed sensitivity analyses by excluding trials with potentially contaminated samples (i.e. patient crossover between groups), quasi and cluster design and in which nurses had full clinical autonomy (to perform tasks) and/or where this information was not reported. For data not combined in meta-analyses, individual trial estimates were compared.

Results

Study identification

A total of 4,133 original records were identified. We excluded 12 of 44 relevant publications for the reasons provided in Table S3 (Additional file 1). Twenty-six studies reported in 32 publications met the inclusion criteria and comprised a total of 38,974 randomised participants (Figure 1) [15-46]. Twenty-four of the studies were RCTs and the other two were economic evaluations based on three of the appraised RCTs [17,26,38]. Table 1 and Table S4 (Additional file 1) report the summary and detailed characteristics of participants, interventions and outcomes of the trials included in review.

Study and population characteristics

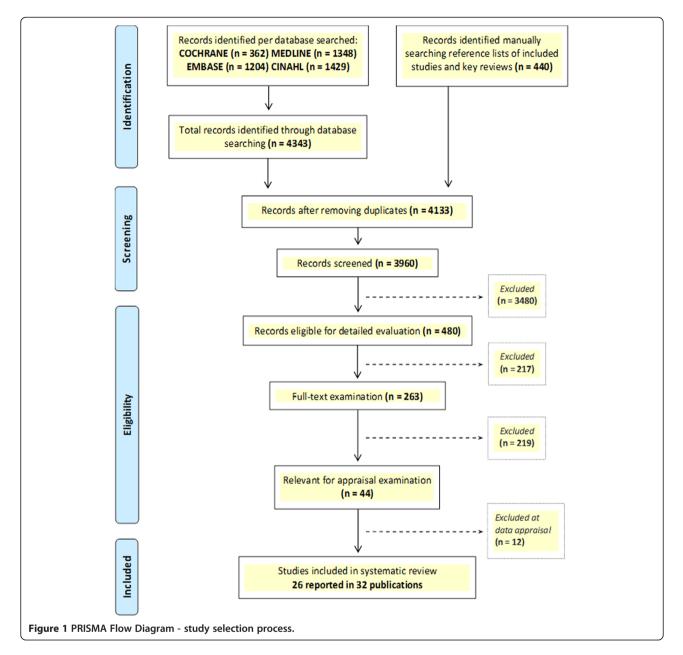
There were twenty RCTs of parallel design, three cluster-RCTs, one quasi-RCT and two studies [31,38] with cost data from three of the included RCTs [17,26,39]. The trials were conducted in the UK (n = 9), the Netherlands (n = 6), the USA (n = 6), Russia (n = 1) and South Africa (n = 2). Median follow-up was 14.8 (range: 0.5 to 122.4) months with at least 12 months in fourteen trials, less than 6 months in seven and 6 to 12 months in the other three. The median number of participants was 1,624 (range: 50 to 12,894) with less than 200 in eleven trials and more than 200 in the other thirteen. Mean age was reported in twenty trials and ranged from 10 to 83 years. Twenty-two trials reported on gender and 38.3% of the participants were male; one included women only.

Settings and interventions

A summary of settings, interventions and nurses' roles are reported in Table 1 and Table S5 (Additional file 1). Nurses worked as physician substitutes in a range of care settings. The interventions were carried-out in general practices [17,18,26,29,30,33,39,44], nurse clinics [23,36,40,42] and in hospital-based, health care centres, specialised practices, community or university clinics [15,16,22,25,27,28,32, 34,35,37,46]. In the controlled intervention, nurses were the main figure of care with autonomous or delegated responsibility in various clinical domains including a whole range of possible (undifferentiated/minor acute/common) or specific conditions (e.g. hypertension, heart failure, diabetes, HIV, etc.). In one trial, the clinical domain was assumed to represent undifferentiated care [35]. Nurses' specific qualifications and training were not reported in sufficient detail but using the information provided by study authors we grouped nurses' roles. Nurses' roles were described in some detail in sixteen trials (two reported in one publication) [15-18,22,23,27-29,32,36,37,39,42,46]. Seven trials employed NP+ only [16,25,28,32,39,40,42], six employed NPs [18,22,26,30,34,44], eight employed RN and/or LN [15,23,27,29,33,35-37], one employed NP and NP+ [17], and one employed NP and LN [46]. Nurses' interventions were guideline- or protocol-based in eighteen trials, while six had no report of having followed specific guidelines. Nurses' clinical autonomy was obtainable from twenty-two trials. In three, nurses had full clinical autonomy to manage patients with diabetes type II [30] or undifferentiated conditions [34,35]. In the other nineteen, nurses made independent decisions to perform several tasks (e.g. adopting, initiating and prescribing treatment, ordering tests or referrals) but they still required minor support or contact with the physicians (e.g. to sign prescriptions, referrals and tests, to discuss patients' records or to develop action plans). Although the interventions in the control group were not clearly described in at least a few trials, these were assumed to represent physicians-usual-led care. Ten trials addressed single contact care [15,39], single contact and on-going care [27,35,37], single contact and urgent care [17,18,26,34] and single, on-going and urgent care [22]. The other fourteen included patients in on-going care for complex conditions (e.g. HIV, Asthma, hypertension, heart failure, etc.).

Risk of bias in the methods of the included studies

The overall quality of the studies varied substantially when assessed against current reporting standards [6,11] (Table 2). Only 54.3% of the trials measured the success of the intervention by defining a primary outcome. Random sequence generation was adequate in 54.0%, allocation concealment in 42.0%, blinding of patients and providers in 4% and blinding of outcome assessors in 21.0%. Patient or clinician crossover between groups was reported in 12.5% of the trials. At baseline, groups were comparable for all tested factors in 70.8% of the trials. Both inclusion and exclusion criteria were reported in 70.8%. Sample size calculation based on power (80.0% to 90.0%) was performed in 70.8%, but only ten trials held the least target sample size to achieve power in at least one outcome. Rates of missing data varied widely (range: 5.0% to 65.5%). While three did not report any attrition, more than half (13/24) of the trials had an attrition rate of at least 20%: nine had more than 20% in both arms in at least one outcome (range: 10.0 to 65.5%), three had at least 45.0% per arm, and four had more than 20% (range: 8.0 to 30.0%) in one arm with a differential rate of 9.0%



to 15.0% across the treatment and control groups. Only 29.2% of the trials reported the use of intention to treat (ITT) techniques (type not always reported) to deal with missing data.

Effectiveness of interventions

Patient satisfaction with quality of care

Patient satisfaction questionnaires were either validated [18,22,26,30], developed for the study purpose [15] or had unclear validation [17,23,37,39]. Meta-analysis of seven studies showed a significant increase in the mean satisfaction scores with nurse-led care (SMD 0.18, 95% CI 0.13 to 0.23) and significant heterogeneity between trials (I² = 91%; χ^2_{6df} = 65.97; p < 0.00001) (Figure 2).

Subgroup analyses by clinical characteristics showed that RN had a stronger effect than NPs in increasing patient satisfaction, although the pooled CIs became wider due to both the smaller number of studies and smaller sample sizes (SMD 1.37, 95% CI 0.88 to 1.85). The effect estimate also increased in studies of single contact care, urgent care visits and shorter (less than 6 months) follow-up episodes, but the significance of the findings did not change. On the other hand, the effect disappeared in studies of on-going care, non-urgent care visits and longer (greater than 6 months) follow-up episodes. Subgroup analyses by study quality showed a more modest estimate with the same level of significance in larger trials, which are less prone to small study bias (N \ge 200:

Study			Setting	Participants	Nurses'	group			Physici	ans' group			Intervention			Out	come	es rep	oorted
Location, first author, year	Design, period [*]	FUP, m	Facilities, n	Included diagnosis	Nurses, n	Patients, N	Mean age (SD), y	Male, %	Phys., n	Patients, N	Mean age (SD), y	Male, %	Nurses' training/ experience	FCA	GDL	PS	QoL	HA	мс
ZA 2 Fairall, 2012 [36], cohort 2	cRCT, 2008- 2010.	18	Nurse ART clinic, 31.	HIV/AIDS.	103	6415	38 (8.9)	30	nr	6479	38 (9.63)	27	Middle nurse managers trained to assume responsibility for ART and established patients' eligibility for ART.	no	yes			1	√
ZA 1 Fairall, 2012 [36], cohort 1	cRCT, 2008- 2010.	16-18	Nurse ART clinic, 31.	HIV/AIDS.	103	6159	36 (9.6)	33	nr	4923	35 (9.63)	31	Middle nurse managers trained to assume responsibility for ART and established patients' eligibility for ART.	no	yes			~	~
NL 6 Houweling, 2011 [30]	RCT, period nr.	14	Practice, 1.	Diabetes Mellitus Type II.	2	116	67.1 (11)	53	5	114	69.5 (10.6)	42	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	1	✓		
NL 5 Kuethe, 2011 [25]	RCT, 2006- 2008.	24	Hospital outpatients, 1; Practice, 18.	Asthma.	nr	36	11.2 (2.9)	64	nr	71 (37 [§] , 34 [‡])	11.2 (2.5) [§] ; 10.1 (2.6) [‡]	58	Asthma nurse.	no	yes		1	1	
RU 1 Andryukhin, 2010 [46]	RCT, 2006 -2009.	6, 18	Medical centre practice, 1.	Heart Failure with Preserved Ejection Fracture.	10	50	66.5 (3.2)	27	8	50	68 (4.3)	34	Nurses with special degree in patient education obtained in a joint course.	no	yes		1	1	√
NL 4 Voogdt-Pruis, 2010 [16]	RCT, 2006- 2007.	12	Healthcare centre, 6.	CVD, Hypertension, Hypercholesterolemia.	6	808	64 (9.0)	58	25	818	64 (9.0)	62	Advance practice nurse already employed to manage patients with asthma, chronic obstructive pulmonary disease, or diabetes.	nr	yes				1
NL 3	RCT, 2006.	0.5	Practice, 15; Reference, 5	Common complaints.	12	817	42.8 (16.5)	38	50/17 [†]	684	46.1 (16.6)	40	Nurse practitioner with Master	no	yes	1	√		V

Table 1 Summary characteristics of participants and interventions of studies included in review

Dierick-Van Dale, 2009 [39]													degree in Advance Nursing trained in common complaints.						
UK 9 Chan, 2009	RCT, 2002- 2004.	6	Nurse clinic, 1	GORD, moderate Gastritis.	nr	89	50.2 (13.9)	49	nr	86	48.4 (12.8)	49	Gastrointestinal nurse practitioner.	no	yes		1		1
[42]									1										
NL 2 Du Moulin, 2007 [37]	cRCT, period nr.	12	nr.	All forms of incontinence.	1	38	51 (13.0)	0	28¶	13	51 (13.0)	0	Registered nurse specialist in incontinence.	no	yes	1	1		
2007 [37] US 6	RCT,	6	Community,	Diabetes Mellitus.	nr	95	55.7	32	108#	102	57 (11.4)	35	Diabetes nurse.	no	yes				1
Hiss, 2007 [32]	period nr.	0	2; PHD, 1.	Diabetes Mellitus.	111	55	(13.1)	52	100	102	57 (11.4)	22	Diabetes nuise.	no	yes				v
NL 1 Hesselink, 2004 [33]	RCT, 2000- 2001.	24	Practice, 12	Asthma and COPD.	2	139	49.9 (14.2)	35	14	137	44.7 (13.6)	28	GP assistant with pre- and during- trial training to deal with the dif- ferences between asthma and COPD.	no	yes		5		
UK 8 Denver, 2003 [40]	RCT, 2000- 2001.	6	Nurse clinic hospital based.	Diabetes Mellitus Type II pre-diagnosed with Hypertension or in receipt of BPLT.	nr	60	58.1 (13.8)	57	nr	60	62.4 (9.1)	70	Hypertension nurse.	no	yes				1
UK 7 Jarman, 2002 [29]	RCT, 1996- 1999.	24	Practice, 438.	Parkinson's Disease.	9	1041	nr	57	nr	818	nr	56	Community nurse with a course in Parkinson Disease.	no	nr		1		J J
UK 6 Kernick, 2002 [27]	RCT, period nr.	4	Health Centre Practice, 1	Asthma	nr	55	Median (IQR): 35 (29-47)	56	9	46	Median (IQR): 37 (27-50)	33	Nurse with structured training in Asthma care.	no	yes		1		
US 5 Mundinger, 2000 [22,24]	RCT, 1995- 1997.	6-12, 24	Community clinic, 4; Primary care clinic, 1.	Asthma, Diabetes Mellitus, Hypertension, or urgent visits.	7	1181	44	24	11	800	44.9	22	Community nurse practitioner.	no	nr	1	1	1	
UK 5 Kernick, 2000 [28]	RCT, period nr.	4	Health Centre, 1	Psoriasis and Eczema.	1	55	47.4 (18.4)	39	nr	54	51.7 (15.8)	48	Practice nurse with training in psoriasis and eczema management.	no	yes		✓		
UK 4 Kinnersley, 2000 [26]	RCT, period nr	0.5-1	Practice, 10	Diverse complaints.	12	₁₄₆₅ ∥	range: 0 to >75	39	10	₁₄₆₅ ∥	range: 0->75	42	Nurse practitioner with diploma on care for same day consultations for primary care.	no	nr	1			
UK 3	RCT, period nr.	0.5	Practice, 20	Diverse complaints: e.g. minor injuries,	20 (1 per practice)	651	nr	42	nr	665	nr	43	Nurse with course at BSc or MSc level.	no	nr	√	1		1

Venning, 2000 [17]				respiratory complaints.															
UK 2	RCT,	0.5	Practice, 5	Acute minor illnesses.	5	900	median	40	19	915	median	40	Practice nurse	no	nr	✓			
Shum, 2000 [18]	1998- 1999.						(IQR):26 (9-41.8)				(IQR):29.1 (9.7-44.9)		with a course in minor illnesses and piloted before study.						
US 4	qRCT,	12	Primary care	Undifferentiated	9	150	62	99	45	300	61	98	Nurse practitioner	yes	yes			✓	\checkmark
Hemani, 1999 [34]	1999- 2001.		veterans affair clinic, 1	conditions.									who was on staff for at least six months in primary care.						
JK 1	RCT,	12,	Practice, 19	Coronary Heart	28	673	66.1	58	nr	670	66.3 (8.2)	58	District and	no	yes		\checkmark	\checkmark	✓ ✓
Campbell, 1998 [19-21,41,43-45]	1995- 1996.	24, 56.4, 122.4		Disease secondary prevention.			(8.2)						practice nurses trained in clinic protocols/GDLs for behavioural techniques change.						
JS 3 Vinter, 1981 15]	RCT, 1980.	0.5	Community clinic, 1	Family planning, venereal diseases, acute non-traumatic minor illnesses.	5	25	nr	nr	5	25	nr	nr	Registered professional nurse with preparation and skills in physical diagnosis, psychosocial assessment, and health-illness man- agement in pri- mary care.	nr	yes	1			
US 2	RCT,	≥6	HO clinic, 1;	Undifferentiated.	4	40	nr	nr	nr	20	nr	nr	Nurse clinicians	yes	nr			√	
Flynn, 1974 [35]	1971.		Private, 3										with training in service delivery.						
US 1	RCT,	12	University	Hypertension, CVD,	nr	33	range:	12	nr	33	range:	12	Nurses who	no	yes	✓	\checkmark	√	\checkmark
Lewis, 1967 [23]	period nr.		Hospital clinic, 1; Nurse clinic, 1	Obesity, Arthritis, Somatization.			16-78				16-83		provided primary source care for at least one year before the study.						

Table 1 Summary characteristics of participants and interventions of studies included in review (Continued)

Legend.

Studies are listed by year (y) of publication, in decreasing order; and labelled after the country where they were conducted.

US, United States; NL, The Netherlands; UK, United Kingdom; ZA, South Africa; RU, Russia; RCT, Randomised Controlled Trial; cRCT, cluster Randomised Controlled Trial; qRCT, quasi-Randomised Controlled Trial; FUP, follow-up episodes are reported in months (m); nr, not reported; ART, Antiretroviral Therapy; PHD, public health department; HO, Hospital Outpatients; HIV, Human Immunodeficiency Virus; CVD, Cardiovascular Disease; GORD, Gastro-Oesophageal Reflux Disease; COPD, Chronic Obstructive Pulmonary Disease; BPLT, Blood Pressure Lowering Treatment; SD, standard deviation; IQR, Interquartile Ranges;

FCA, full clinical autonomy; GDL, interventions based on clinical guidelines or protocols; PS, patient satisfaction; QoL, quality of life; HA, hospital admissions; M, mortality; C, costs.

^{*}Start and end year when studies were conducted.

[†]Reference practices for comparison on economic/cost data.

[‡]Paediatricians.

[§]General physicians.

Number of randomized patients per group not reported.

[¶]Nine were physicians and nineteen were supervisors.

[#]Sixty-three were for the control group.

Table 2 Quality of methods in the studies included in review

Study details (country,	Inclusion &	Outo	ome	Sequence	Allocation	Blinding	Sample	Attrition	Funding
design, funding)	exclusion criteria	1ry	2ry	generation	concealment		size	%	
ZA 2	\checkmark	\checkmark	\checkmark	А	А	NP^{\ddagger}	√∥	≥20 [#]	G
Fairall, 2012 [36] (Cohort 2)									
ZA 1	\checkmark^{\dagger}	\checkmark	\checkmark	А	А	NP^{\ddagger}	√∥	≥20#	G
Fairall, 2012 [36] (Cohort 1)									
NL 6	\checkmark^{\dagger}	\checkmark	\checkmark	I	А	NP	\checkmark	<20	G
Houweling, 2011 [30]									
NL 5	\checkmark^{\dagger}	\checkmark		А	А	NP	\checkmark^{\P}	<20	NR
Kuethe, 2011 [25]									
RU 1	\checkmark			U	I	ŧ	\checkmark^{\P}	≥20	None
Andryukhin, 2010 [46]									
NL 4	\checkmark	\checkmark		А	U	l ^{‡,§}	\checkmark	<20	P/Ind.
Voogdt-Pruis, 2010 [16]									
NL 3	\checkmark^{\dagger}			А	А	NP	NP	≥20	G
Dierick-Van Dale, 2009 [39]									
UK 9	\checkmark^{\dagger}			А	А	NP [§]	\checkmark	<20#	NR
Chan, 2009 [42]									
NL 2	\checkmark^{\dagger}	\checkmark	\checkmark	U	U	NP	\checkmark^{\parallel}	≥20	NR
Du Moulin, 2007 [37]									
USA 6	×			U	U	NP	NP	<20	G
Hiss, 2007 [32]									
NL 1	*	\checkmark	\checkmark	U	U	NP [§]	\checkmark^{\parallel}	≥20	NR
Hesselink, 2004 [33]									
UK 8	*	\checkmark	\checkmark	I	I	NP	√ ¶	<20#	NR
Denver, 2003 [40]									
UK 7	\checkmark	\checkmark	\checkmark	А	А	NP	\checkmark	<20	P/Ind.
Jarman, 2002 [29]									
UK 6	*†	\checkmark	\checkmark	А	U	U	\checkmark	≥20 [#]	NR
Kernick, 2002 [27]									
US 5	*			U	U	NP	√ ¶	≥20	G
Mundinger, 2000 [22,24]									
UK 5	\checkmark	\checkmark		А	U	U	√ [¶]	≥20	Ind.
Kernick, 2000 [28]									
UK 4	\checkmark	1	\checkmark	А	А	NP	✓ ^{⊠,¶}	≥20	G
Kinnersley, 2000 [26]									
UK 3	\checkmark			А	А	NP	NR ^{,¶}	≥20	Р
Venning, 2000 [17]									
UK 2	\checkmark			А	А	NP	\checkmark^{\P}	≥20	G
Shum, 2000 [18]									
US 4	\checkmark			I	I	NP	NP	U	NR
Hemani, 1999 [34]									
UK 1	\checkmark			А	I	NP§	\checkmark	≥20#	G
Campbell, 1998 [19-21,41,43-45]									
US 3	\checkmark	1		U	U	A [‡]	NR	U	NR

Table 2 Quality	y of methods in the	studies included in	n review (Continued)
-----------------	---------------------	---------------------	----------------------

Winter, 1981 [15]							
US 2	*	U	U	NP	NR	<20	NR
Flynn, 1974 [35]							
US 1	*	U	U	NP§	NR	U [#]	G
Lewis, 1967 [23]							

Legend.

Studies are listed by year (y) of publication, in decreasing order. Blinding: whether patients, care providers and outcome assessors were blinded. *Attrition* of more than 20% is of significant concern. *Intention to treat* (ITT) whether study authors analysed all patients based on their original group allocation regardless of protocol violations or non-compliance. US, United States; NL, The Netherlands; UK, United Kingdom; ZA, South Africa; RU, Russia; I, Inadequate; A: Adequate; U, Unclear; NP, Not Performed; NR, Not reported; Funding, Government (G), Industry (Ind.) or Private (P) grant.

^{*}Only the inclusion criteria was reported.

[†]Not all factors tested at baseline were comparable between groups.

⁺Fairall et al. (2012) [36] partly blinded data analysts; Andryukhin et al. (2010) [46] blinded clinicians not patients; Voogdt-Pruis et al. (2010) [16] blinded patients not clinicians; Winter (1981) [15] blinded patients and clinicians.

[§]Outcome assessors blinded for some or all outcomes.

[⊠]Used a cluster effect approach (e.g. Huber-White).

[¶]Reached the least target sample required to achieve power.

[#]Used ITT strategies to deal with missing data.

Study/Subgroup	RCTs,	, Nurse	es,	Physician	5,	IV, Fixed	-	SMD (95%CI)	Н	eterog	geneity		Overall
	n	Mean (SD)	Ν	Mean (SD)	Ν		%		Chi²	df	Р	I²,%	effect, P
A) all trials													
, Mundinger, 2000		4.45 (0.89)	644	4.46 (0.89)	389		17.3	-0.01 (-0.14 to 0.11)					
Dierick-van Daele, 2009		8.19 (1.18		8.2 (1.26)				-0.01 (-0.12 to 0.10)					
Shum, 2000		78.6 (16)	635	76.4 (17.8)		T_		0.13 (0.02 to 0.24)					
Venning, 2000		4.4 (0.5)	608	4.22 (0.5)	571	-		0.36 (0.24 to 0.47)					
Kinnersley, 2000		77.9 (9.5)	334	74.0 (9.2)	596	-		0.42 (0.28 to 0.55)					
DuMoulin, 2007		8.7 (1)	35	7.5 (1)	10			1.18 (0.43 to 1.93)					
Winter, 1981		94.78 (9)	25	74.03 (17)	25			1.50 (0.87 to 2.14)					
Overall (95% CI)	7	54.70 (5)	2964	/4.05 (17)	2857			0.18 (0.13 to 0.23)	65 97	6 4	0 00001	91	<0.0000
,						Y		,		•			
3) subgroup													
Employed nurses													
NP	3		1613		1642	•		0.16 (0.09 to 0.23)			0.0001		< 0.0000
NP+	2		1291		1180	•	-	0.17 (0.09 to 0.25)			0.00001	95	<0.000
RN	2		60		35			1.37 (0.88 to 1.85)	0.42	1	0.52	0	<0.0000
Type of care single contact	5		2285		2458			0.21 (0.16 to 0.27)	10 00	1 -0	0.00001	02	<0.0000
ongoing care	2		679		399	•		0.02 (-0.10 to 0.15)			0.000	92 89	0.73
urgent care visits	4		2221		2213	•		0.22 (0.16 to 0.28)			0.00001		<0.0000
non-urgent visits	3		743		644	•		0.06 (-0.05 to 0.17)					0.28
Follow-up													
<6 months	5		2285		2458	•		0.21 (0.16 to 0.27)	48.99	4 <c< td=""><td>0.00001</td><td>92</td><td><0.0000</td></c<>	0.00001	92	<0.0000
≥6 months	2		679		399	+		0.02 (-0.10 to 0.15)	9.47	1 (0.002	89	0.73
Study size													
N≤200	2		60		35			1.37 (0.88 to 1.85)	0.42	1	0.52	0	< 0.0000
N>200	5		2904		2822	•		0.16 (0.11 to 0.22)	42.08	4 <c< td=""><td>0.00001</td><td>90</td><td>< 0.0000</td></c<>	0.00001	90	< 0.0000
Risk of bias*													
adequate concealment	4		2260		2433	•		0.20 (0.14 to 0.26)	32.96	3 <0	0.00001	91	<0.0000
inadequate concealment	3		704		424	+		0.08 (-0.05 to 0.20)	29.66	2 <0	0.00001	93	0.22
					-2	-1 0	1 2						
					Pot	er with PLC Bet	ter with NLC						

Figure 2 Effects of physician-nurse substitution on patient satisfaction in A) all trials and by B) subgroups. Legend. CI, confidence interval; df, degrees of freedom; N, total number of patients; SMD, standard mean differences; SD, standard deviation; Chi², statistical test for

heterogeneity; P, p-value of Chi² (evidence of heterogeneity of intervention effects); I^2 , amount of heterogeneity between trials; Overall P, p-value for significance of effects of interventions; NLC, Nurse-Led Care; PLC, Physician-Led Care; NP, Nurse Practitioner; NP+, Nurse Practitioner with higher degree/courses/specialisation; RN, Registered Nurse. *All trials had \geq 20% attrition in at least one arm.

Study/Subgroup	RCTs,	Nurses	Physicians		IN	/, Fixed		Weight	RR(95%CI)			rogene		Overall
	n	N/Total	N/Total					%		Chi²	df	Р	l²,%	effect, F
A) all trials														
Shum, 2000		1/684	3/694					0.6	0.34 (0.04 to 3.24)					
Campbell, 1998		106/540	145/518					66.3	0.70 (0.56 to 0.87)					
Andryukhin, 2010		9/44	10/41					5.1	0.84 (0.38 to 1.85)					
Mundinger, 2000		68/800	50/509					26.4	0.87 (0.61 to 1.23)					
Flynn, 1974		10/40	2/20					1.6	2.50 (0.60 to 10.34)					
Overall (95% CI)	5	194/2108	210/1782					100	0.76 (0.64 to 0.91)	4.30	4	0.37	7	0.003
B) subgroups						•								
Employed nurses														
NP	3	175/2024	198/1721			•			0.74 (0.62 to 0.89)	1.47	2	0.48	0	0.001
RN/LN	2	19/84	12/61			+			1.09 (0.54 to 2.17)	1.73	1	0.19	42	0.81
Type of care														
single contact	3	79/1524	55/1223			•			0.90 (0.64 to 1.26)	2.76	2	0.25	27	0.53
ongoing care	2	115/584	155/559			•			0.71 (0.57 to 0.88)	0.18	1	0.67	0	0.002
urgent care visits	2	69/1484	53/1203			-			0.85 (0.60 to 1.19)	0.65	1	0.42	0	0.34
non-urgent visits	3	125/624	157/579			•			0.73 (0.59 to 0.90)	3.13	2	0.21	36	0.003
Follow-up*														
<12 months	4	48/1568	42/1264			•			0.74 (0.49 to 1.12)	3.94	3	0.27	24	0.16
≥12 months	3	183/1384	205/1068			•			0.75 (0.63 to 0.90)	1.09	2	0.58	0	0.002
Study size														
N≤200	2	19/84	12/61			-			1.09 (0.54 to 2.17)	1.73	1	0.19	42	0.81
N>200	3	175/2024	198/1721			•			0.74 (0.62 to 0.89)	1.47	2	0.48	0	0.001
Risk of bias														
adequate concealment	1	1/684	3/694						0.34 (0.04 to 3.24)	NA				0.35
inadequate concealment	4	193/1424	207/1088			•			0.76 (0.64 to 0.91)	3.81	3	0.28	21	0.003
<20% attrition	1	10/40	2/20						2.50 (0.60 to 10.34)	NA				0.21
≥20% attrition	4	184/2068	208/1762			•			0.75 (0.62 to 0.89)	1.56	3	0.67	0	0.001
			(0.01	0.1	1	10	100						
				Lo	wer with NL	с	Lower with	n PLC						
igure 3 Effects of phy	sician-	nurse subst	itution on l	hospita	al admiss	ions in	A) all tri	als and	by B) subgroups	. Lege	nd.	Cl, co	nfide	nce
terval; df, degrees of fre				•										
r heterogeneity; P, p-v														

interval; df, degrees of freedom; N, number of patients with events; Total, total number of patients per group; RR, Relative Risk; Chi², statistical test for heterogeneity; P, p-value of Chi² (evidence of heterogeneity of intervention effects); I², amount of heterogeneity between trials; Overall P, p-value for significance of effects of interventions; NLC, Nurse-Led Care; PLC, Physician-Led Care; NP, Nurse Practitioner; NP+, Nurse Practitioner with higher degree/courses/specialisation; RN, Registered Nurse. ^{*}Two RCTs provided data for different follow-up episodes and were incorporated accordingly: Andryukhin et al. (2010) [46] reported data at 6 and 18 months and Mundinger et al. (2000) [22,24] reported data at 6 and 12 months.

SMD 0.16, 95% CI 0.11 to 0.22; N < 200: SMD 1.37, 95% CI 0.88 to 1.85). The effect was not significant in trials with inadequate allocation concealment. All trials had at least 20% attrition. Heterogeneity disappeared in the subgroup of registered nurses and smaller trials (N < 200). Two other trials with qualitative data reported significantly higher patient satisfaction scores with nurse-led care [23,30].

Hospital admissions

Five trials had sufficient data for meta-analysis (Figure 3), two of which reported different follow-up episodes [22,46]. The pooled RR showed a significant reduction in the risk of all-cause hospital admissions with nurse-led care (RRs 0.76, 95% CI 0.64 to 0.91) and no significant heterogeneity between trials ($I^2 = 7\%$; $\chi^2_{3df} = 4.30$; p = 0.37). Subgroup analyses by clinical characteristics showed that NPs had a positive effect in reducing all-cause admissions to hospital (RRs 0.74, 95% CI 0.62 to

0.89) while the effect was not significant with RNs. The estimate increased in studies of on-going care, nonurgent visits and longer (at least 12 months) follow-up episodes. The effect disappeared in trials of single contact care, urgent care and shorter (less than 12 months) follow-up episodes. Subgroup analyses by study quality showed that in large trials (less prone to bias) nurse-led care had an increasingly significant effect in reducing hospital admissions (N < 200: RR 1.09, 95% CI 0.54 to 2.17; N \geq 200: RR 0.74, 95% CI 0.62 to 0.89). However, trials that were of higher quality in other ways (e.g. better allocation concealment and less attrition) tend to show the opposite effect with better quality being associated with higher rates of admissions with nurse-led care, albeit non-significant. Heterogeneity remained non-significant across subgroups and disappeared in studies of nurse practitioners, on-going and urgent care, longer follow-up episodes, larger trials and trials with at least 20% attrition. In addition, data that were not pooled showed less

tudy/Subgroup	RCTs, n	Nurses N/Total	Physicians N/Total		IV, Fixed		Weight %	RR(95%CI)		Hete df	rogene P	eity I²,%	Overall effect, I
) all trials													
Hiss, 2007		0/95	3/102				0.2	0.15 (0.01 to 2.93)					
Voogdt-Pruis, 2010		1/314	7/387					0.18 (0.02 to 1.42)					
Shum, 2000		0/684	2/694 —			_		0.20 (0.01 to 4.22)					
Hesselink, 2004		0/115	1/94 —				0.1	0.27 (0.01 to 6.62)					
Denver, 2003		0/60	1/60 _				0.1	0.33 (0.01 to 8.02)					
Hemani, 1999		3/150	9/300				0.4	0.67 (0.18 to 2.43)					
Campbell, 1998		100/673	128/670					0.78 (0.61 to 0.99)					
Jarman, 2002		353/1016	307/803					0.91 (0.80 to 1.03)					
Fairall, 2012)		997/4943	747/3407					0.92 (0.85 to 1.00)					
Andryukhin, 2010		2/44	2/41					0.93 (0.14 to 6.31)					
Overall (95% CI)	10	1456/8094	1207/6558		♦		100	0.89 (0.84 to 0.96)	7.52	9	0.58	0	0.001
B) subgroups													
Employed nurses													
NP	3	103/1507	139/1664		•			0.76 (0.60 to 0.96)	0.8	2	0.67	0	0.02
NP+	3	1/469	11/549					0.19 (0.04 to 0.85)	0.15	2	0.93	0	0.03
RN/LN	4	1352/6118	1057/4345		•			0.92 (0.85 to 0.98)	0.58	3	0.9	0	0.01
Type of care													
single contact	2	3/834	11/994					0.53 (0.17 to 1.70)	0.51	1	0.48	0	0.29
ongoing care	8	1453/7260	1196/5564		•			0.90 (0.84 to 0.96)	6.38	7	0.5	0	0.001
urgent care visits	1	0/684	2/694					0.20 (0.01 to 4.22)	NA				0.3
non-urgent visits	9	1456/7410	1205/5864		•			0.90 (0.84 to 0.96)		8	0.58	0	0.001
Follow-up*													
<12 months	4	1/883	8/897					0.26 (0.07 to 1.06)	0.4	3	0.94	0	0.06
≥12 months	7	1456/7255	1201/5702		•			0.90 (0.84 to 0.96)			0.57	0	0.002
Study size													
N≤200	4	5/349	15/503	-				0.54 (0.21 to 1.36)	1.21	3	0.75	0	0.19
N>200	6	1451/7745	1192/6055		•			0.90 (0.84 to 0.96)	5.54	5	0.35	10	0.002
Risk of bias													
adequate concealment	3	1350/6643	1056/4904		•			0.92 (0.85 to 0.98)	0.97	2	0.61	0	0.01
inadequate concealment	7	106/1451	151/1654		•			0.73 (0.58 to 0.91)	3.83	6	0.7	0	0.006
<20% attrition	4	354/1485	318/1352		•			0.89 (0.78 to 1.00)	4.18		0.24	28	0.05
≥20% attrition	6	1102/6609	889/5206		↓			0.90 (0.83 to 0.97)			0.64	0	0.008
			0.01	0.1	1	10	100						
			0.01	Lower with N		wer with PLC	100						
			ostitution on mo										

freedom; N, number of patients with events; Total, total number of patients per group; RP, Relative Risk; Chi², statistical test for heterogeneity; P, p-value of Chi² (evidence of heterogeneity of intervention effects); I², amount of heterogeneity between trials; Overall P, p-value for significance of effects of interventions; NLC, Nurse-Led Care; PLC, Physician-Led Care; NP, Nurse Practitioner; NP+, Nurse Practitioner with higher degree/courses/ specialisation; RN, Registered Nurse. Andryukhin et al. (2010) [46] reported data at 6 and 18 months and was incorporated accordingly.

hospital admissions with nurse-led care [23,36] or no significant differences between groups [22,44,36] (see Additional file 1: Table S7). Qualitative data reported less hospital admissions with nurse-led care at 24 months [25] or no significant differences between groups at 1 month [26] or 12 months [34].

Mortality

Ten trials had sufficient data for meta-analysis, one of which reported different follow-up episodes [46] (Figure 4). The pooled RRs showed a significant reduction in the risk of all-cause mortality with nurse-led care (RRs 0.89, 95% CI 0.84 to 0.96) and no significant heterogeneity between trials ($I^2 = 0\%$; $\chi^2_{9df} = 7.52$; p = 0.58). Subgroup analyses by clinical characteristics showed that NPs had an increased effect but less significant than RN/LN in reducing all-cause mortality (NP: RRs 0.76, 95% CI 0.60 to 0.96;

RN/LN: RRs 0.92, 95% CI 0.85 to 0.98). Although NPs+ showed an increased estimate, the CIs were wide and less significant (RR 0.19, 95% CI 0.04 to 0.85). The estimate increased in studies of on-going care, non-urgent visits and longer (at least 12 months) follow-up episodes but the CIs and significance remained the same. The effect disappeared in trials of single contact, urgent care visits (n = 1)and shorter (less than 12 months) follow-up episodes. The estimate increased, although with wider CIs and less significance, in trials with inadequate allocation concealment (RRs 0.73, 95% CI 0.58 to 0.91) and in trials with at least 20% attrition (RRs 0.90, 95% CI 0.83 to 0.97). On the other hand, the estimate decreased, with reduced significance, in trials of adequate concealment and trials of less than 20% attrition and disappeared in small trials (N < 200, RR 0.54, 95% CI 0.21 to 1.36). Heterogeneity between trials remained non-significant in all subgroups

Wundinger, 2000 0.02 0.0638 220 165 0.02 (-0.11 to Wundinger, 2000 0.02 0.095 649 391 0.02 (-0.18 to) SF-12 The second seco	rr, 2000 0.02 0.0638 220 165 1,7 2000 0.02 0.0995 649 391 0.02 (-0.11 to 0.15) -0.01 (-0.22 to 0.20) 0.02 (-0.18 to 0.22) 9 0.07 0.02 0.0995 649 391 0.02 (-0.18 to 0.22) 9 9 0.7 0.05 0 0.06 0.0689 455 0 0.06 (-0.08 to 0.20) 0 0.06 0.0689 455 0 0.06 (-0.08 to 0.20) 0 0.06 (-0.17 to 0.05) 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Scale / Study	SMD	SE	Nurses patients, N	Physicians patients, N					SMD(95%CI)
Mundinger, 2000 0.02 0.0638 220 165 0.02 {-0.11 to Mundinger, 2000 0.01 0.1046 222 184 -0.01 {-0.22 to Mundinger, 2000 0.02 0.0995 649 391 0.02 {-0.11 to String 0.05 0.056 89 86 0.070 (0.40 to String 0.06 0.0699 455 415 0.06 {-0.070 (0.40 to String 0.06 0.0561 696 558 -0.06 {-0.17 to String 0.02 {-0.13 to 0.2245 35 46 -0.22 {-0.15 {-0.59 to String 0.02 {-0.15 {-0.59 to 0.26 {-0.15 {-0.59 to -0.15 {-0.59 to -0.15 {-0.59 to String 0.02 {-0.15 {-0.55 to 0.16 {-0.0561 696 558 -0	rr, 2000 0.02 0.099 649 391 0.02 0.02 0.099 649 391 0.02 0.02 0.099 649 391 0.02 0.02 0.02 0.099 649 391 0.02 0.02 0.03 0.02 0.099 649 391 0.02 0.02 0.03 0.02 0.099 649 391 0.02 0.02 0.03 0.02 0.099 649 391 0.02 0.02 0.03 0.02 0.00 0.02 0.00 0.05 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	F-36									
Wundinger, 2000 -0.01 0.1046 222 184 -0.01 (-0.22 to 0) Wundinger, 2000 0.02 0.0995 649 391 -0.02 (-0.18 to 0) SF-12 Than, 2009 0.7 0.1556 89 86 -0.00 (-0.00 to 0) Europol 5D (0-6dead,1=full health) Dierick-van Daele, 2009 0.06 0.0689 456 415 -0.06 (-0.08 to 0) Europol 5D (0.59=worst,1= best) Iarman, 2002 -0.06 0.0277 35 10 -0.02 (-0.18 to 0) Europol 5D (v.59=worst,1= best) Iarman, 2002 -0.06 0.227 35 46 -0.02 (-0.18 to 0) Europol 5D by VAS Dubudulin, 2007 0.12 0.3597 35 46 -0.32 (-0.76 to 0) Clinical score for Eczema and Psoriasis Europol 5D (-0.59 to 1) 0.2245 35 46 -0.02 (-0.13 to 0) Global General Questionnaire for Parkinson's Disease Iarman, 2002 0.0561 696 558 -0.02 (-0.13 to 0) Respiratory Illness Questionnaire (RIQ) -0.12 0.1531 115 94 0.06 (-0.21 to 0) Harman, 2002 0.06 0.1403 96	r, 2000 0.02 0.0995 649 391 0.02 (0.18 to 0.22) 9 0.07 0.1556 89 86 0.002 (0.18 to 0.22) 9 0.07 0.1556 89 86 0.006 (0.08 to 0.00) D (0-dead,1=full health) n 0 aele, 2009 0.06 0.0689 456 415 0.066 (0.08 to 0.00) D (0-59=worst,1= best) 002 0.06 0.0561 696 558 0.006 (0.17 to 0.05) D by VAS 1, 2007 0.12 0.3597 35 10 0.02 (0.28 to 0.82) 000 0.026 0.227 35 46 0.02 (0.18 to 0.20) D gy Life Quality Index 000 -0.32 0.2245 35 46 0.02 (0.05 to 0.20) meral Questionnaire for Parkinson's Disease 002 0.016 0.0561 696 558 0.000 (0.05 to 0.20) Parkinson's Disease 002 0.016 0.0561 696 558 0.000 (0.05 to 0.20) Parkinson's Disease 002 0.016 0.0561 696 558 0.000 (0.05 to 0.20) Parkinson's Disease 002 0.016 0.0561 696 558 0.000 (0.02 (0.13 to 0.09) ry Illness Questionnaire (RQ) 2.004 0.021 0.1531 115 94 0.000 (0.05 to 0.21) Parkinson's Disease 002 0.056 0.0561 558 0.000 (0.05 to 0.27) Parkinson's Disease 002 0.0561 558 0.000 (0.0561 558 0.000 (0.0561 558 0.000 (0.0561 558 0.000 (0.0561 558 0.000 (0.0561	Houweling, 2011	0.15	0.1505	85	93			-		0.15 (-0.14 to 0.44)
Aundinger, 2000 0.02 0.0995 649 391 0.02 (0.18 to 1000) if:12	r, 2000 0.092 0.0995 649 391 0.02 (-0.18 to 0.22) 9 0.7 0.1556 89 86 0.70 (0.40 to 1.00) D (0-dead, 1-full health) 0.06 0.0689 456 415 0.06 (-0.08 to 0.20) D (0-59=worst, 1= best) 0.02 0.06 0.0561 696 558 0.06 (-0.17 to 0.05) D by VAS	Aundinger, 2000	0.02	0.0638	220	165			•		0.02 (-0.11 to 0.15)
1-12 The set of the	9 0.7 0.1556 89 86 - 0.70 (0.40 to 1.00) D (0-dead_1-full health)	Aundinger, 2000	-0.01	0.1046	222	184		+	•		-0.01 (-0.22 to 0.20)
han, 2009 0,07 0,1556 89 86 0,00 (0,00 to uroqol 5D (0-dead, 1=full health) ierick-van Daele, 2009 0,06 0,0689 456 415 0,006 (-0.08 to uroqol 5D (V-S5=worst, 1= best) arman, 2002 0,06 0,0561 696 558 0,006 (-0.07 to uroqol 5D VAS unoqol 5D V	D (0-dead,1=full health) in Daele, 2009 0.06 0.0689 456 415 0.06 (-0.08 to 0.20) 0.059=worst,1= best) 002 -0.06 0.0561 696 558 -0.06 (-0.17 to 0.05) 0.12 (-0.58 to 0.20) 0.026 0.227 35 46 -0.22 (-0.18 to 0.70) 0.26 (-0.18 to 0.70) 0.20 0.05 0.16 0.0561 696 558 0.16 (-0.05 to 0.2) 0.15 (-0.59 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.18 to 7.0 0.20 0.06 0.140 96 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.06 (-0.17 to 0.3) 0.11 (-0.13 to 0.6) 0.21 (-0.30 to 0.6) 0.20 (-0.40 to 0.5) 0.20 (-0.	Aundinger, 2000	0.02	0.0995	649	391			+		0.02 (-0.18 to 0.22)
uroqol SD (0-dead, 1=full health) 0.06 0.0689 456 415 0.06 (-0.08 to 1) uroqol SD (-0.59=worst, 1= best) arman, 2002 -0.06 0.0561 696 558 -0.06 (-0.17 to 1) uroqol SD by VAS 0.12 0.3597 35 10 -0.26 (-0.18 to 1) permich, 2000 0.26 0.227 35 46 -0.32 (-0.76 to 1) permich, 2000 -0.32 0.2245 35 46 -0.15 (-0.59 to 1) ichnick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 1) ichnick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 1) ichnick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 1) ichnick, 2000 -0.16 0.0561 696 558 -0.02 (-0.13 to 1) ichnick, 2000 -0.02 0.0561 696 558 -0.02 (-0.13 to 1) ichnick, 2004 0.016 0.1531 115 94 0.21 (-0.09 to 1) ichnicestorinaire -0.02 0.6819922 40 35 -0.64 (-0.72 to 1) ichn	D (0-dead,1=full health) in Daele, 2009 0.06 0.0689 456 415 0.06 (-0.08 to 0.20) 0.059=worst,1= best) 002 -0.06 0.0561 696 558 -0.06 (-0.17 to 0.05) 0.12 (-0.58 to 0.20) 0.026 0.227 35 46 -0.22 (-0.18 to 0.70) 0.26 (-0.18 to 0.70) 0.20 0.05 0.16 0.0561 696 558 0.16 (-0.05 to 0.2) 0.15 (-0.59 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.18 to 7.0 0.20 0.06 0.140 96 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.16 (-0.05 to 0.2) 0.16 (-0.0561 696 558 0.06 (-0.17 to 0.3) 0.11 (-0.13 to 0.6) 0.21 (-0.30 to 0.6) 0.20 (-0.40 to 0.5) 0.20 (-0.	F-12									
tierick-van Daele, 2009 0.06 0.0689 456 415 0.066 0.05 10 0.0680 456 415 0.066 (-0.17 to uroqol 5D (-0.59=worst, 1= best) arman, 2002 -0.06 0.0561 696 558 -0.06 (-0.17 to uroqol 5D by VAS uudoulin, 2007 0.12 0.3597 35 10 0.12 (-0.58 to 0.226 0.227 35 46 0.226 (-0.18 to 0.26 (-0.15 to 0.226 0.55 35 46 -0.02 (-0.15 (-0.59 to 0.26 (-0.15 (-0.59 to 0.26 (-0.15 (-0.59 to 0.26 (-0.18 to 0.26 (-0.18 to 0.26 (-0.15 (-0.59 to 0.26 (-0.15 (-0.26 (-0.15 (-0.26 (-0.15 (-0.26 (-0.15 (-0.26 (-0.15 (-0.26 (-0.15 (-0.26	n Daele, 2009 0.06 0.0689 456 415 0.06 (-0.08 to 0.20) D (-0.59=worst,1= best) 002 -0.06 0.0561 696 558 0.06 (-0.17 to 0.05) D by VAS , 2007 0.12 0.3597 35 10 0.026 (-0.18 to 0.70) 003 0.26 0.227 35 46 0.026 (-0.18 to 0.70) 003 0.02 0.2245 35 46 0.022 (-0.18 to 0.70) 003 -0.15 0.2245 35 46 0.012 (-0.59 to 0.22) meral Questionnaire for Parkinson's Disease 002 0.16 0.0561 696 558 0.016 (0.05 to 0.27) Parkinson' Disease 002 0.02 0.0561 696 558 0.016 (0.05 to 0.27) Parkinson' Disease 002 0.02 0.0561 696 558 0.016 (0.05 to 0.27) Parkinson' Disease 002 0.02 0.0561 696 558 0.012 0.012 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) , 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) , 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a LVing with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 0.66(-0.21 to 0.31) a LVing with Heart Failure Questionnaire in, 2010 1.307 1.0878 55 46 0.064 0.020 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.020 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.020 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.000 0.064 0.010 0.000 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.064 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.020 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.020 0.064 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.064 0.070 0.064 0.070 0.064 (-0.72 to 2.00) 004 0.06 0.1403 96 80 0.064 (-0.72 to 2.00) 004 0.06 0.1403 96 80 0.064 (-0.72 to 2.00) 004 0.06 0.1408 95 80 0.064 (-0.72 to 2.00) 005 0.064 (-0.72 to 2.00) 004 0.06 0.1408 95 80 0.064 (-0.72 to 2.00) 005 0.064 (-0.72 to 2.00) 006 0.064 0.070 0.069 0.069 0.069 0.069 0.069 0.069 0.069 0.060 0	han, 2009	0.7	0.1556	89	86			-		0.70 (0.40 to 1.00)
uraged SD (-0.59-worst, 1= best) -0.06 0.0561 696 558 -0.06 (-0.17 to) uraged SD by VAS -0.02 0.3597 35 10 -0.02 (-0.18 to) uraged SD (-0.227 35 46 -0.02 (-0.18 to) -0.02 (-0.18 to) ernick, 2000 -0.32 0.2245 35 46 -0.32 (-0.76 to) inical score for Eczema and Psoriasis ernick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to) ilobal General Questionnaire for Parkinson's Disease -0.02 0.0561 696 558 -0.02 (-0.13 to) griman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to) espiratory Illness Questionnaire for Parkinson's Disease -0.02 0.0561 696 558 -0.02 (-0.13 to) esselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to) 0.06 (-0.21 to) innensota Living with Heart Failure Questionnaire -0.639 (-0.592 40 35 -0.64 (-0.72 to) 1.31 (-0.30 to) sthma related QoL instrument (ARQoL) -0.639 (-0.6921 55 46 -2 0 2 4 <td>D (-0.59=worst,1= best) D (-0.12 (-0.58 to 0.82) D (-0.12 (-0.58 to 0.12) D (-0.12 (-0.59 to 0.12) D (-0.15 (-0.59 to 0.29) meral Questionnaire for Parkinson's Disease D (-0.15 (-0.59 to 0.29) meral Questionnaire for Q (-0.15 (-0.59 to 0.29) meral Questionnaire for Q (-0.15 (-0.59 to 0.29) Parkinson's Disease D (-0.2 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) . 2004 0.21 0.1531 115 94 . 2004 0.06 0.1403 96 80 a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 </td> <td>uroqol 5D (0=dead,1=full health)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	D (-0.59=worst,1= best) D (-0.12 (-0.58 to 0.82) D (-0.12 (-0.58 to 0.12) D (-0.12 (-0.59 to 0.12) D (-0.15 (-0.59 to 0.29) meral Questionnaire for Parkinson's Disease D (-0.15 (-0.59 to 0.29) meral Questionnaire for Q (-0.15 (-0.59 to 0.29) meral Questionnaire for Q (-0.15 (-0.59 to 0.29) Parkinson's Disease D (-0.2 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) . 2004 0.21 0.1531 115 94 . 2004 0.06 0.1403 96 80 a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 	uroqol 5D (0=dead,1=full health)									
arman, 2002 -0.06 0.0561 696 558 -0.06 (-0.17 to 1) uroqol 5D by VAS 0.12 0.3597 35 10 0.12 (-0.58 to 0) ernick, 2000 0.26 0.227 35 46 0.26 (-0.18 to 0) termatology Life Quality Index -0.05 (-0.15 to 0) 0.2245 35 46 -0.32 (-0.76 to 0) termick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 0) ilobal General Questionnaire for Parkinson's Disease -0.02 (-0.15 to 0) -0.02 (-0.15 to 0) -0.02 (-0.15 to 0) arman, 2002 0.16 0.0561 696 558 -0.02 (-0.13 to 0) espiratory Illness Questionnaire (RIQ) -0.02 0.0561 696 558 -0.02 (-0.13 to 0) tesselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0) 0.06 (-0.21 to 0) timesota Living with Heart Failure Questionnaire -0.6819922 40 35 -0.64 (-0.72 to 0) 1.04 (-1.10 to 0) ernick, 2002 0.6396 0.6921 55 46 -0.64 (-0.72 to 0) 1.04 (-1.10 to 0) ernick, 2002 1.037	002 -0.06 0.0561 696 558 -0.06 (-0.17 to 0.05) Db y VAS .2007 0.12 0.3597 35 10 0.12 (-0.58 to 0.82) 000 0.26 0.227 35 46 0.26 (-0.18 to 0.70) ogy Life Quality Index 0.000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0.12) ore for Eczema and Psoriasis 0.016 0.0561 696 558 0.16 (0.05 to 0.27) neral Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 0.06 0.1403 96 558 0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.21 0.1531 115 94 0.06 (-0.21 to 0.33) 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire (RIQ) .2004 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 1.04 (-1.10 to	ierick-van Daele, 2009	0.06	0.0689	456	415		I			0.06 (-0.08 to 0.20)
unroad 5D by VAS 0.12 0.3597 35 10 0.12 (-0.58 to) uMoulin, 2007 0.26 0.227 35 46 0.26 (-0.18 to) ernick, 2000 -0.32 0.2245 35 46 -0.32 (-0.76 to) inical score for Eczema and Psoriasis -0.15 0.2245 35 46 -0.15 (-0.59 to) ilobal General Questionnaire for Parkinson's Disease -0.16 0.0561 696 558 -0.16 (0.05 to) q-39 for Parkinsons' Disease -0.22 0.0561 696 558 -0.02 (-0.13 to) espiratory Illness Questionnaire (RIQ) esselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to) lesselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to) timesota Living with Heart Failure Questionnaire (RQOL) -0.392 40 35 -0.44 (-0.72 to) ernick, 2002 0.6396 0.6921 55 46 -0.64 (-0.72 to) ernick, 2002 1.037 1.0878 55 46 -0.44 (-2 -2 0 2 4	Db VAS 0.12 0.3597 35 10 0.12 (-0.58 to 0.82) 000 0.26 0.227 35 46 0.26 (-0.18 to 0.70) ogy Life Quality Index 000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0.12) ore for Eczema and Psoriasis 000 -0.15 0.2245 35 46 -0.35 (-0.59 to 0.29) interal Questionnaire for Parkinson's Disease 002 0.16 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) 0.021 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.21 0.130 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 0.6819922 40 35 1.31 (-0.03 to 2.64) .2004 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 0.64 (-0.72 to 2.00) .002 1.037 1.0878 55 46	uroqol 5D (-0.59=worst,1= best)									
uMoulin, 2007 0.12 0.3597 35 10 0.12 (-0.58 to 0) ernick, 2000 0.26 0.227 35 46 0.26 (-0.18 to 0) ermitology Life Quality Index ernick, 2000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0) linical score for Eczema and Psoriasis ernick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 0) diobal General Questionnaire for Parkinson's Disease arman, 2002 0.16 0.0561 696 558 -0.02 (-0.13 to 0) espiratory Illness Questionnaire (RQ) esselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0) lesselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0) 0.06 (-0.21 to 0) Ininesat Living with Heart Failure Questionnaire ndryukhin, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to 0) sthma related QoL instrument (ARQoL) ernick, 2002 0.6396 0.6921 55 46 -0.64 (-0.72 to 0) ernick, 2002 1.037 1.0878 55 46 -0.24 (-0.10 to 0) -0.64 (-0.72 to 0)	2007 0.12 0.3597 35 10 0.12 (-0.58 to 0.82) 000 0.26 0.227 35 46 0.26 (-0.18 to 0.70) ogy Life Quality Index 000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0.12) ore for Eczema and Psoriasis 000 -0.15 0.2245 35 46 -0.15 (-0.59 to 0.29) inneral Questionnaire for Parkinson's Disease 002 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 002 -0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire	arman, 2002	-0.06	0.0561	696	558					-0.06 (-0.17 to 0.05)
ernick, 2000 0.26 0.227 35 46 0.26 (-0.18 to 1 ermatology Life Quality Index ernick, 2000 -0.32 0.2245 35 46 -0.32 (-0.76 to 1 linical score for Eczema and Psoriasis ernick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 1 lobal General Questionnaire for Parkinson's Disease trman, 2002 0.16 0.0561 696 558 0.16 (0.05 to 1 	000 0.26 0.227 35 46 0.26 (-0.18 to 0.70) ogy Life Quality Index 000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0.12) ore for Eczema and Psoriasis 000 -0.15 0.2245 35 46 -0.15 (-0.59 to 0.29) ore for Eczema and Psoriasis 000 -0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 002 -0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Ilhess Questionnaire (RIQ) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire	uroqol 5D by VAS									
termatology Life Quality Index -0.32 0.2245 35 46 -0.32 (-0.76 to 10.0000) linical score for Eczema and Psoriasis -0.15 0.2245 35 46 -0.15 (-0.59 to 10.0000) idobal General Questionnaire for Parkinson's Disease -0.16 0.0561 696 558 -0.16 (0.05 to 10.0000) Q-39 for Parkinsons' Disease -0.02 0.0561 696 558 -0.02 (-0.13 to 10.0000) garman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to 10.0000) gespiratory Illness Questionnaire (RIQ) -0.02 0.0561 159 -0.02 (-0.13 to 10.0000) esselink, 2004 0.21 0.1531 115 94 -0.21 (-0.09 to 10.0000) disselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to 10.0000) filmesota Living with Heart Failure Questionnaire -0.6819922 40 35 -0.64 (-0.72 to 10.01000) sthma related QoL instrument (ARQoL) -0.6396 0.6921 55 46 -0.64 (-0.72 to 10.04 (-1.10 to 10.04 (-1	oog Life Quality Index 000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0.12) ore for Eczema and Psoriasis 000 -0.15 0.2245 35 46 -0.15 (-0.59 to 0.29) one ral Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.02 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.02 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to	uMoulin, 2007	0.12	0.3597	35	10			-		0.12 (-0.58 to 0.82)
emick, 2000 -0.32 0.2245 35 46 -0.32 (-0.76 to 1) linical score for Eczema and Psoriasis -0.15 0.2245 35 46 -0.15 (-0.59 to 1) ilobal General Questionnaire for Parkinson's Disease -0.16 0.0561 696 558 0.16 (0.05 to 0) Q-39 for Parkinsons' Disease -0.02 0.0561 696 558 -0.02 (-0.13 to 1) espiratory Illness Questionnaire (RIQ) -0.02 0.1531 115 94 -0.21 (-0.09 to 1) esselink, 2004 0.21 0.1531 115 94 0.06 (-0.21 to 1) filmesota Living with Heart Failure Questionnaire 0.06 0.1403 96 80 -0.02 (-0.13 to 1) ernick, 2002 0.6396 0.6921 55 46 -0.21 (-0.09 to 1) 0.06 (-0.21 to 1) sthma related QoL instrument (ARQoL) 1.3052 0.6819922 40 35 -0.64 (-0.72 to 1) 1.04 (-1.10 to 1) ernick, 2002 0.6396 0.6921 55 46 -0.24 (-2) 0 2 4	000 -0.32 0.2245 35 46 -0.32 (-0.76 to 0.12) ore for Eczema and Psoriasis -0.15 0.2245 35 46 -0.15 (-0.59 to 0.29) oneral Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease -0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) -0.06 0.1403 96 80 0.06 (-0.21 to 0.31) , 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 1.31 (-0.03 to 2.64) 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 002 0.6396 0.6921 55 46 -0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 -0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 -0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 -0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 -0.64 (-0.72 to 2.00) 0.04 0.05	ernick, 2000	0.26	0.227	35	46					0.26 (-0.18 to 0.70)
Linical score for Eczema and Psoriasis ernick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 1 lobal General Questionnaire for Parkinson's Disease arrman, 2002 0.16 0.0561 696 558 0.16 (0.05 to 1 Q-39 for Parkinsons' Disease arrman, 2002 -0.02 0.0561 696 558 0.002 (-0.13 to 1 espiratory Illness Questionnaire (RIQ) esselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to 1 esselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to 1 tinnesota Living with Heart Failure Questionnaire ndryukhin, 2010 1.3052 0.6819922 40 35 0.64 (-0.72 to 1 sthma related QoL instrument (ARQoL) ernick, 2002 0.6396 0.6921 55 46 0.64 (-0.72 to 1 1.04 (-1.10 to 1 -4 -2 0 2 4	ore for Eczema and Psoriasis 0.15 0.2245 35 46 -0.15 (-0.59 to 0.29) eneral Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 0.02 -0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) <td< td=""><td>ermatology Life Quality Index</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	ermatology Life Quality Index									
errick, 2000 -0.15 0.2245 35 46 -0.15 (-0.59 to 1) ilobal General Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 1) Q-39 for Parkinsons' Disease -0.02 0.0561 696 558 -0.02 (-0.13 to 1) graman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to 1) lespiratory Illness Questionnaire (RIQ)	000 -0.15 0.245 35 46 -0.15 (-0.59 to 0.29) eneral Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 0.02 0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) .2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) .2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire .2004 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 0.21 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.21 0.519 0.55 46 -2 0 2 4	ernick, 2000	-0.32	0.2245	35	46			ł		-0.32 (-0.76 to 0.12)
Silobal General Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 0.05 to Q-39 for Parkinsons' Disease -0.02 0.0561 696 558 -0.02 (-0.13 to 1) arman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to 1) tespiratory Illness Questionnaire (RIQ) 10.1531 115 94 0.21 (-0.09 to 1) tesselink, 2004 0.21 0.1531 115 94 0.06 (-0.21 to 1) Alinnesota Living with Heart Failure Questionnaire undryukhin, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to 1) Asthma related QoL instrument (ARQoL) 1.037 1.0878 55 46 0.64 (-0.72 to 1) 1.04 (-1.10 to 1)	Ameral Questionnaire for Parkinson's Disease 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 0.002 0.002 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) , 2004 0.21 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 Etter with PLC Better with NLC										
arman, 2002 0.16 0.0561 696 558 0.16 (0.05 to parkinsons' Disease arman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to parkinsons' Disease arman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to parkinsons' Disease arman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to parkinsons' Disease Arman, 2004 0.21 0.1531 115 94 0.21 (-0.09 to parkinsons' Disease Hesselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to parkinsons' Disease Vinnesota Living with Heart Failure Questionnaire	002 0.16 0.0561 696 558 0.16 (0.05 to 0.27) Parkinsons' Disease 0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) vy Illness Questionnaire (RIQ) 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.02 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 0.24 (-0.10 to 3.17) Better with PLC Better with NLC Better with NLC Better with NLC	Kernick, 2000	-0.15	0.2245	35	46		-	-		-0.15 (-0.59 to 0.29)
PQ-39 for Parkinsons' Disease arman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to Respiratory Illness Questionnaire (RIQ) Hesselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to tesselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to Vinnesota Living with Heart Failure Questionnaire Andryukhin, 2010 1.3052 0.6819922 40 35 Asthma related QoL instrument (ARQoL) Kernick, 2002 0.6396 0.6921 55 46 0.64 (-0.72 to 1.037 1.0878 55 46 0.64 (-0.72 to 1.04 (-1.10 to	Parkinsons' Disease 002 -0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) 2 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) 2 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 002 0.6396 0.6921 55 46 0.664 (-0.72 to 2.00) 1.037 1.0878 55 46 0.664 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	Global General Questionnaire for Parkinson's	5 Disease								
arman, 2002 -0.02 0.0561 696 558 -0.02 (-0.13 to l) Respiratory Illness Questionnaire (RIQ) -0.21 0.1531 115 94 0.21 (-0.09 to l) Hesselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to l) Vinnesota Living with Heart Failure Questionnaire 0.3052 0.6819922 40 35 -1.31 (-0.03 to l) Asthma related QoL instrument (ARQoL) 0.6396 0.6921 55 46 -0.64 (-0.72 to l) Kernick, 2002 1.037 1.0878 55 46 -4 -2 0 2 4	002 -0.02 0.0561 696 558 -0.02 (-0.13 to 0.09) ry Illness Questionnaire (RIQ) 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.037 1.0878 55 46 0.64 (-0.72 to 2.00) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.04 -1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.50 -2 0 2 4 -2 0 2 4 Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	arman, 2002	0.16	0.0561	696	558					0.16 (0.05 to 0.27)
Respiratory Illness Questionnaire (RIQ) 4esselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to 10) 4esselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to 10) Vinnesota Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 10) Asthma related QoL instrument (ARQoL) 4 0.037 1.0878 55 46 0.64 (-0.72 to 10) Kernick, 2002 1.037 1.0878 55 46 0.64 (-0.72 to 10) 1.04 (-1.10 to 10)	ry Illness Questionnaire (RIQ) , 2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) , 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	Q-39 for Parkinsons' Disease									
itesselink, 2004 0.21 0.1531 115 94 0.21 (-0.09 to 1) itesselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to 1) Vinnesota Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 1) Asthma related QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 1) Gernick, 2002 1.037 1.0878 55 46 0.64 (-0.72 to 1) -4 -2 0 2 4	2004 0.21 0.1531 115 94 0.21 (-0.09 to 0.51) 2004 0.06 0.1403 96 80 0.06 (-0.21 to 0.33) a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.4 (-1.10 to 3.17) Better with PLC Better with PLC Better with PLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life.	arman, 2002	-0.02	0.0561	696	558			•		-0.02 (-0.13 to 0.09)
lesselink, 2004 0.06 0.1403 96 80 0.06 (-0.21 to 1.010) Alinnesota Living with Heart Failure Questionnaire undryukhin, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to 1.010) ststmar related QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 1.010) ernick, 2002 1.037 1.0878 55 46 0.64 (-1.10 to 1.010)	2004 0.06 0.1403 96 80 0.06 0.02 to 0.33 a Living with Heart Failure Questionnaire 1.3052 0.6819922 40 35 1.31 (-0.03 to 2.64) elated QoL instrument (ARQoL) 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00)	espiratory Illness Questionnaire (RIQ)									
Alinnesota Living with Heart Failure Questionnaire undryukhin, 2010 1.3052 0.6819922 40 35 1.31 (-0.03 to Asthma related QoL instrument (ARQoL) ternick, 2002 0.6396 0.6921 55 46 0.64 (-0.72 to ternick, 2002 1.037 1.0878 55 46 0.64 (-0.72 to 1.04 (-1.10 to -4 -2 0 2 4	a Living with Heart Failure Questionnaire in, 2010 1.3052 0.6819922 40 35 elated QoL instrument (ARQoL) 002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.02 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 0.04 -2 0 2 4 Better with PLC Better with PLC Better with PLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life.	lesselink, 2004	0.21	0.1531	115	94			-		0.21 (-0.09 to 0.51)
Andryukhin, 2010 1.3052 0.6819922 40 35 40 35 46 46 46 46 40 1.31 (-0.03 to 1.31 (-0.03 to 1.31 (-0.02 to 1.04 (-0.72 to 1.04 (-1.10 to -4 -2 0 2 4	in, 2010 1.3052 0.681992 0.681992 0.681992 0.681992 0.681992 0.681992 0.681992 0.681992 0.681992 0.681992 0.68192 0.68192 0.68192 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.691 0.691 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.692 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) 0.64 0.	lesselink, 2004	0.06	0.1403	96	80		-	+		0.06 (-0.21 to 0.33)
Asthma related QoL instrument (ARQoL) iernick, 2002 0.6396 0.6921 55 46 0.64 (-0.72 to iernick, 2002 1.037 1.0878 55 46 0.64 (-0.72 to -4 -2 0 2 4	elated QoL instrument (ARQoL) 002 0.6396 0.6921 55 46 002 1.037 1.0878 55 46 -4 -2 0 2 4 Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	-							_		
Xernick, 2002 0.6396 0.6921 55 46 0.64 (-0.72 to Xernick, 2002 1.037 1.0878 55 46 0.64 (-0.72 to -4 -2 0 2 4	002 0.6396 0.6921 55 46 0.64 (-0.72 to 2.00) 002 1.037 1.0878 55 46 0.64 (-0.72 to 2.00) 1.04 (-1.10 to 3.17) -4 -2 0 2 4 Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	Andryukhin, 2010	1.3052	0.6819922	40	35					1.31 (-0.03 to 2.64)
Xernick, 2002 1.037 1.0878 55 46 1.04 (-1.10 to -4 -2 0 2 4	002 1.037 1.0878 55 46 1.04 (-1.10 to 3.17) -4 -2 0 2 4 Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	Asthma related QoL instrument (ARQoL)									
-4 -2 0 2 4	-4 -2 0 2 4 Better with PLC Better with NLC Comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled	Kernick, 2002	0.6396	0.6921	55	46			-		0.64 (-0.72 to 2.00)
	Better with PLC Better with NLC	ernick, 2002	1.037	1.0878	55	46			-	<u> </u>	1.04 (-1.10 to 3.17)
	Better with PLC Better with NLC						-4	-2	1 0	2	4
State wanted Beach wanted	comparison of individual trial estimates of the effect of physician-nurse substitution on Quality of Life. Legend. A pooled										
ure E Comparison of individual trial actimates of the effect of physician purse substitution on Quality of Life Legend A peop		ure E Comparison of individual tri	al actimator	of the offer	t of physici						

although low heterogeneity was introduced in trials with less than 20% attrition and smaller trials. The funnel plot was asymmetrical showing five trials falling to the left (nurse-led care with fewer events), two on the right and three on the line of no effect. Data that could not be pooled showed a significantly lower cumulative rate of all-cause mortality and a marginal significance in the cumulative rate of mortality due to coronary/non-fatal myocardial infarction with nurse-led care at 56.4 months [44] (Additional file 1: Table S7). Qualitative data reported to have no documentation of death after 12 months follow-up [36].

Sensitivity analyses

In the meta-analyses (Figures 2, 3 and 4), excluding the studies in which nurses had full clinical autonomy or from which this information was not obtainable did not critically alter the estimates (Additional file 1: Table S6). The small

non-significant amount of heterogeneity in the metaanalysis of hospital admissions was attributable to a small study which favoured physician-led care but had wide CIs. Excluding quasi-RCTs or cluster RCTs from the metaanalyses of patient satisfaction and mortality slightly reduced the pooled estimate but did not alter the direction of effects and the findings remained significant.

Random-effects meta-analyses

Meta-analyses using a RE model showed the same direction of effect. The pooled estimates and heterogeneity remained significant. Patient satisfaction showed an increased estimate although wider CIs (SMD 0.31, 95% CI 0.12 to 0.514, p = 0.002; I² = 91%; χ^2_{6df} = 65.97; p < 0.0001). Hospital admissions (RRs 0.77, 95% CI 0.63 to 0.94, p = 0.01; I² = 7%; χ^2_{4df} = 4.30; p = 0.37) and mortality (RRs 0.90, 95% CI 0.84 to 0.96, p = 0.002; I² = 0%; χ^2_{9df} = 7.52;

Subgroup/Study		Nurses,		Phy	sicians,		IV, Fix	ed	SMD(95%CI)
	Mean	(SD)	N	Mean	(SD)	Ν			
Direct costs - all patients									
Dierick-van Daele, 2009*	31.94	(36.29)	747	40.15	(49.94)	650	-		-0.19 (-0.30 to -0.08
Dierick-van Daele, 2009 ⁺	144.4	(53.18)	747	145.87	(67.15)	650	+		-0.02 (-0.13 to 0.08
Direct costs - patients <65 years									
Dierick-van Daele, 2009 [‡]	161.57	(33.98)	747	170.75	(46.58)	650	-		-0.23 (-0.33 to -0.12
Dierick-van Daele, 2009⁵	161.57	(33.98)	747	168.9	(46.58)	650	-		-0.18 (-0.29 to -0.08
Dierick-van Daele, 2009∥	161.57	(33.98)	747	170.1	(46.58)	650	-		-0.21 (-0.32 to -0.11
Direct costs - total costs of clinicia	ns								
Venning, 2000¶	11.71	(25.23)	641	14.14	(29.62)	651	-		-0.09 (-0.20 to 0.02
Venning, 2000 [#]	17.69	(33.41)	641	20.68	(33.41)	651	-		-0.09 (-0.20 to 0.02
Venning, 2000**	18.11	(33.43)	641	20.7	(33.43)	651	-		-0.08 (-0.19 to 0.03
Venning, 2000 ⁺⁺	11.29	(25.18)	641	14.11	(29.63)	651	-		-0.10 (-0.21 to 0.01
Costs per patient for drug treatme	nt at 6m follov	v up							
Chan, 2009 ^{‡‡}	35.5	(48.8)	89	71.7	(63.1)	89			-0.64 (-0.94 to -0.34
Cost per Quality of Life Years									
Campbell, 1998§§	3.18	(0.69)	673	3.05	(0.69)	670		•	0.19 (0.08 to 0.30
Direct cost: study practices vs. a ex	ternal referen	ce							
Dierick-van Daele, 2009∥∥	35.76	(43.35)	1397	39.21	(42.99)	1350	+		-0.08 (-0.15 to -0.01
Dierick-van Daele, 2009¶¶	165.69	(40.37)	1397	168.25	(40.48)	1350	+		-0.06 (-0.14 to 0.01
Dierick-van Daele, 2009##	145.08	(60.07)	1397	141.09	(63.03)	1350	+		0.06 (-0.01 to 0.14
						-4	-2 0	2	4
							Cheaper with NLC	Cheaper with PLC	

Figure 6 Comparison of individual trial estimates of the effect of physician-nurse substitution on cost of care. Legend. A pooled estimate was not possible due to the variety in approaches, currency and indicators used to value resources and to calculate costs. Abbreviations: EUR, Euro; GBP, pound sterling; DCC, direct costs for consultations; DPCC, direct and productivity costs for consultations; general physicians (GP); EMP, employment; EMPO, employment by others; LoC, length of consultations; TCT, total consultation time; TP, time to prescribe; FTF, face-to-face; TT, total time; SD, standard deviation; N, total number of patients per group; SMD, standard mean difference; CI, confidence interval; NLC, Nurse-Led Care; PLC, Physician-Led Care. *EUR; DPCC: GPs salary in EMP and EMPO; p = 0.65. [†]EUR; DCC based on resource use, follow-up, LoC /salary; p = 0.0001. [§]EUR; all patients: DPCC: GP salary in EMP and EMPO; p = 0.009. ^{II}EUR; <65 years: DPCC: GP salary in EMP and EMPO; p < 0.0001. [§]GBP; return consultations, FTF time: NP = TCT - TP (GP signed); GP = TCT + TP; p = 0.11. ^{#*}GBP; initial consultations, TT: NP = TCT - TP (GP signed); GP = TCT + TP; p = 0.10. ^{#*}GBP; mean QALYs at 48 months: SF-36 overall QoL scores; p = 0.0006. ^{III}EUR; DPCC: resource use, follow-up, LoC and salary; p = 0.004. ^{##}EUR; CC: resource use, follow-up, LoC and salary; p = 0.004.

p = 0.58) showed very similar estimates of a more modest but yet significant effect.

Quality of life

Four [27-29,37] of the thirteen [17,22,23,27-30,33,37, 39,42,44,46] trials with measures on QoL used both disease-specific and generic scales of functional health and well-being. Other seven [17,22,23,30,39,42,44] used only generic scales and two used only disease-specific scales [33,46]. Due to the different scales, grading scores and measurements, we decided not to combine trials in a pooled analysis (Figure 5). Comparison of the individual estimates of trials using generic scales showed nurse-led care significantly improved QoL scores with the SF-12 at 6 months (SMD 0.70, 95% CI 0.40 to 1.00) and with the Global General Questionnaire for Parkinson's Disease at 24 months

(SMD 0.16, 95% CI 0.05 to 0.27). Estimates from trials using the SF-36 and Eurogol did not reach significance although some favoured nurse-led care. Trial estimates [27,33,46] using disease-specific scales at 4, 6, 12, and 24 months favoured nurse-led care but were not significant. Four trials reported better scores with nurse-led care in various individual dimensions of the AROoL, SF-36 and RIO guestionnaires but the overall score was not significant at two weeks [45] or not sustained at least 12 month thresholds [27,33,44] except for patients with incontinence for whom better scores of individual dimensions at 6 months persisted at 12 months or reached a significant overall score (reported p < 0.05 [37]. Qualitative data based on generic scales reported significance (general health questionnaire) [23] or non-significance (SF-36, EQ5D-VAS) in the overall score at 0.5 [17] or at 4 [27] months.

Costs

There were six trials [17,23,29,35,42,44] with data on cost and two [31,38] comprehensive economic evaluations. Due to the large variety of approaches used to value the resources and calculate cost we didn't pool trials in a meta-analysis. Figure 6 shows the comparison of the individual trial estimates. Costs were generally lower with nurse-led care in direct costs including consultations within study practices, for all patients and in patients not yet 65 years old, in study practices (compared to external reference practices) [38] at 0.5 or 12 [23] months, and in treatment costs with both unadjusted and adjusted data at 6 months [42]. On the other hand, the mean cost per quality adjusted life years (QALYs) at the end of 56.4 months and the cost of interventions (clinics and drugs) were significantly higher with nurse-led care in one trial [44]. Another trial showed lower costs with nurse-led care based on face-to-face total cost of clinicians (total consultation time without the time to get prescriptions signed by physicians or time taken to sign a prescription) [17]. The studies also showed no significant differences between nurses and physicians in direct and productivity costs for consultations in all patients at study practices [38], direct and productivity costs for consultations in all patients or for patients not yet 65 years old at study practices (compared to external reference practices) [38], in the costs of care based on either the total time or face-toface time given by the nurse or physician [17] or other healthcare system costs (hospitals, outpatient attendances and admissions to private hospitals) [44].

Other trials reported lower healthcare costs with nurseled care at 6 to 56.4 months [23,35,44] and no significant differences between groups in net healthcare costs [29].

Discussion

Substitution of physicians by nurses is often discussed and widely practiced in many countries, with the aim of satisfying the demands of an aging population and (local) shortages of physicians. Our review showed that the volume of rigorous evaluations is slowly increasing but remains low. In addition, the quality of available research does allow strong recommendations for practice and policy, despite previous proposals [6,7].

In the appraised literature, the nurses assessed a wide variety of conditions and performed various tasks, with different degrees of clinical autonomy and in different settings. Despite this heterogeneity and the substantial methodological limitations, our review suggested that nurse-led care is associated with higher patient satisfaction, lowered overall mortality and lowered hospital admissions. Effects on other outcomes, such as QoL and costs remained inconclusive.

The effect of nurse-led care on hospital admissions and mortality was particularly present in studies of ongoing care and non-urgent visits and when nurse practitioners (both NP and NP with higher degree/courses) provided the care. This suggests that trained nurses can effectively provide healthcare to patients with established diseases. However, the effect disappeared (for hospital admissions) or weakened (for mortality) in studies with better or adequate concealment of allocation and in larger studies. The reasons for this surprising and important finding, especially that nurse-led care could lead to reduced mortality, should be addressed in future studies.

Our overall results also showed a highly significant effect of nurse-led care on patient satisfaction although with severe heterogeneity between trials. This finding is consistent with previous reviews [3,4]. Nevertheless, this result should be interpreted with caution. Although the average effect is positive, subgroups of patients reported less positive views. Our results suggest this variability may be due to nurses' roles or study size, which may be associated with other factors (such as degree of clinical autonomy). The effect disappeared when we considered only the trials based on on-going care or non-urgent care, and in trials with longer follow-up episodes (at least 6 months), but these subgroups included two trials only. Surprisingly, patient satisfaction was higher with general nurses (as compared to NPs or NPs with higher degree/extra courses), but the two very small studies showing this effect addressed tasks for very special conditions such as incontinence and family planning. This finding fits in with previous research which showed that patients appreciate nurses' involvement especially in education and counselling [47,48].

The results on QoL were difficult to interpret due to heterogeneous reporting of outcomes and the data that were scattered across different scales with outcome measurements at variable follow-up time intervals. Only a few trials used both generic and disease-specific scales with primarily one trial per scale. There was a potential increase in QoL scores with nurse-led care, when health status was evaluated using generic scales, or for specific conditions (e.g. heart failure, Parkinson's Disease) but the effect was not significant or not sustained at length (at least 12 months) or it was contradicted by data from the same studies [28]. Similarly, there were some effects of lower costs with nurse-led care, but the reported data used different approaches to value the resources and to calculate costs in only a few trials and economic evaluations.

Methodological appraisal of included studies

We identified several significant limitations in the current evidence which should be considered in future research. The trials included were highly heterogeneous in terms of tasks, settings, collection and reporting of outcome measurements. There is a considerable amount of data that are reported in descriptive accounts only, limiting both their pooled validity and the interpretation of their results. Additionally, many studies failed to report some important statistical information (e.g. sample sizes, mean scores, SDs) required to calculate trial estimates and to integrate them in a meta-analysis.

No study fulfilled the set of methodological quality criteria assessed, despite widely available guidelines for RCTs. Trials of lower methodological quality (small study, at least 20% attrition and lack/unclear allocation concealment) tended to inflate the results and only less than 50% of the trials maintained the least target sample required to achieve power, which makes results less trustworthy. The most probable small study bias affecting the effect sizes are the results of small negative studies which are generally less likely to be published than small studies with positive results (i.e. publication bias). Blinding (clinicians, patients and outcome assessors) was reported in only a few trials and we don't rule out the possibility that patient satisfaction, a subjective outcome, may have been especially positively affected by this. The trials consisted of follow-up episodes of variable length (0.5 to 122.4) months) which may have limited the true effect of care especially in multi-morbid or serious illnesses. Our analyses partly explained the reasons for heterogeneity where this was present but several other variables, which we could not account for, may have also caused this. Patients' perception and evaluation of satisfaction may be inherently subjective due to socio-demographic differences, experiences from previous care, the physical environment, and patient-care provider interactions. Therefore, measurements of outcome using validated tools are preferred. Of the trials appraised, less than 50% used validated questionnaires for patient satisfaction.

We also identified a lack of trials of cluster randomisation. Although these may be more complex in design, if accounted for all key factors including clustering effect, appropriate sampling and analyses, cluster RCTs could add important value to the current evidence.

Surprisingly, there is a dearth of economic data. The little evidence available on the cost of physician-nurse substitution relies on results which are mainly based on direct costs and use variable approaches. The more recent literature reports more economic data, but it seems difficult to integrate these results especially because cost evaluations differ across countries and thus in cost measurements. We found only two publications [31,38] providing economic data related to three of the included trials. Despite continued claims of substituting physicians by nurses based on healthcare costs, the evidence can only suggest that substitution is cost neutral. Therefore, as suggested in a recent systematic review of economic evaluations [49], to meaningfully place the costs and consequences of substitution in the context of healthcare, studies should address all types of costs. Relevant and appropriate data should be generated by means of a systematic collection of economic measures, and specific rules for cost data estimations should also be defined and followed.

More intensive implementation could enhance the outcomes of nursing care, but most studies do not provide the necessary information. In the evaluated studies, the assumption is that nurses possess the competence required for substituting physicians, but the level of substitution does not seem equal among studies. While the level of training may be a critical factor for an effective outcome, the studies report incomplete descriptions of nurses' roles and competencies. The level of clinical autonomy in nurses does not seem consistent with the level of training and the tasks performed. Also, nurses still require support or communication with the physician for various tasks. It seems then that the level of qualification and training required to carry out substitution requires yet a better definition of practice boundaries including a classification of tasks. Better criteria conceptualised to define nurses' roles and responsibilities are needed. In addition, the various differences between countries' definitions and their organisation of nurse care should be taken into account. Lastly, more than half of the evidence reviewed (62.5%) has been conducted in Europe, mainly the UK and the Netherlands.

It is apparent that there is much room for primary studies that include larger numbers of patients, methodologically more rigorous in terms of quality, comprehensive in terms of data and statistical methods and with longer follow-up episodes. Furthermore, in order to gain a better understanding of substitution, future research should map a wider range of nurses, the various levels of training and clinicians' characteristics, which are provided in many countries. As suggested previously [50], each method of skill-mix may have its own strengths and weaknesses. The implementation of methodologies aiming at the standardisation of skill-mix studies could support a sound assessment such that health sector reform may also benefit from the publication of evidence.

Strengths and limitations of the review

Our review updates and extends earlier systematic reviews [3,4] and benefits from a thorough assessment of RCTs, in which the nurse acted as the main figure of care. It also presents (where available) the results by nurses' roles. Having used the fixed effect model, we can only make inferences about the studies included in the meta-analyses performed here. We only included RCTs because these are at a lower risk of bias and allow for the identification of causal relationships. Although non-randomised trials may overestimate the benefits of

nurse-led care it would be recommended to scrutinise the current evidence with such designs. These may not only provide an opportunity for an update but also allow for the collection of data from long term (more than 12 months) follow-up designs which may consist of larger sample sizes. We only included publications in English. We did however screen the reference lists of relevant reviews (some in foreign languages) and searched the reference lists of all included studies. We did not contact authors for further information nor did we search for grey literature. A further limitation is that it was often difficult to understand in detail what role and responsibilities nurses had, when substituting physicians. In many cases, they remain embedded in patient care teams that also involved physicians.

Conclusion

The slowly growing number of studies, assessing substitution of physicians by nurses is still substantially limited by methodological deficiencies. Also, the current evidence belongs to a small selection of healthcare systems lacking good quality data. Nevertheless, nurse-led care seems to have a positive effect on hospital admissions and mortality. This important finding should be confirmed and the determinants of this effect should be assessed in future studies. Before implementing new changes in the delivery of healthcare, further, larger and more methodically rigorous primary research should address the quality of the data on both health outcomes and costs. Primary research should also differentiate between types of nurses, qualifications and tasks. In particular, we recommend considering the role of multidisciplinary teams in which nurses are embedded, also when substituting physicians in specific clinical tasks.

Additional file

Additional file 1: List of Tables supporting the results of studies included in review. Table S1: PRISMA Checklist. Table S2: Search strategy in Ovid Medline. Table S3: Studies excluded with reasons for exclusion based on appraisal of full text articles. Table S4: Characteristics of participants and interventions in the included studies. Table S5: Summary of nurses' roles, clinical autonomy and type of care. Table S6: Sensitivity analyses. Table S7: Individual trial estimates from data not combined in meta-analyses.

Competing interests

The authors declare no competing interests.

Authors' contributions

NAMG: design and analyses of the study; conceptualisation of the study; design and formulation of search strategies; screening of titles, abstracts and full texts; acquisition of the data; planning of the analysis and interpretation of data; quality assessment; wrote and revised the manuscript. SD: contribution to the design and conceptualisation of the study; screening of titles, abstracts and full texts; acquisition of data and quality assessment. RT: contribution to the design and conceptualisation of the study; support clinical input on eligibility of studies; and on extraction of reported clinical

data. FH-G: contribution to the design and conceptualisation of the study; screening of titles, abstracts and full texts; quality assessment and data extraction. SM: contribution to the consensus of data. MW: contribution with revision of the manuscript. TR: senior supervision of the study, oversaw the development and methodology of the review; input on eligibility of studies and on the interpretation of the data; revision of the manuscript. All authors read and approved the final version of the manuscript to be published.

Acknowledgements

We thank Fran Mikulicic for his support in the initial stage of the search strategies and Oliver Senn for his support with statistical queries.

Funding

This study was funded by the Health Services Research Fund (Bangerter foundation) from the Swiss Academy of Medical Sciences (SAMS) and by the Swiss Association of Family Physicians (Hausärzte Schweiz) which had no involvement in the content or preparation of the present manuscript.

Author details

¹Institute of Primary Care, University Hospital Zurich, Pestalozzistrasse 24, 8091 Zurich, Switzerland. ²Scientific Institute for Quality in Healthcare, Radboud University Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, Netherlands.

Received: 25 June 2013 Accepted: 10 March 2014 Published: 12 May 2014

References

- 1. World Health Organization: *World Health Statistics 2012: Indicator Compendium.* Geneva, Switzerland: WHO; 2012.
- World Health Organization: Task Shifting: Rational Redistribution of Tasks among Health Workforce Teams: Global Recommendations and Guidelines. Geneva, Switzerland: WHO; 2008.
- 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, 2:CD001271.
- Horrocks S, Anderson E, Salisbury C: Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. *BMJ* 2002, 324:819–823.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: 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.
- 6. Juni P, Altman DG, Egger M: Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001, **323**:42–46.
- Juni P, Witschi A, Bloch R, Egger M: The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999, 282:1054–1060.
- Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011, 343:d5928.
- 9. Fergusson D, Aaron SD, Guyatt G, Hebert P: Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002, **325**:652–654.
- Review Manager: (RevMan) [Computer program] Version 5.2.4 for Windows edition. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2012. http://tech.cochrane.org/revman.
- Higgins JPT, Green S (Eds): Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. http://www.cochrane-handbook.org.
- 12. Chinn S: A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med* 2000, **19**:3127–3131.
- 13. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002, 21:1539–1558.
- Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP: Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011, 11:d4002. doi:10.1136/bmj. d4002.
- 15. Winter C: *Quality health care: patient assessment*. MSc Thesis: California State University; 1981.

- Voogdt-Pruis HR, Beusmans GHMI, Gorgels APM, Kester ADM, Van Ree JW: Effectiveness of nurse-delivered cardiovascular risk management in primary care: A randomised trial. Br J Gen Pract 2010, 60:40–46.
- 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, 320:1048–1053.
- Shum C, Humphreys A, Wheeler D, Cochrane MA, Skoda S, Clement S: Nurse management of patients with minor illnesses in general practice: multicentre, randomised controlled trial. *BMJ* 2000, **320**:1038–1043.
- 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 randomised controlled trial. *BMJ* 2005, 330:707.
- 20. Murchie P, Campbell NC, Ritchie LD, Simpson JA, Thain J: Secondary prevention clinics for coronary heart disease: four year follow up of a randomised controlled trial in primary care. *BMJ* 2003, **326**:84.
- 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, 21:567–574.
- Mundinger MO, Kane RL, Lenz ER, Totten AM, Tsai WY, Cleary PD, Friedewald WT, Siu AL, Shelanski ML: Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. JAMA 2000, 283:59–68.
- 23. Lewis CE, Resnik BA: Nurse clinics and progressive ambulatory patient care. N Engl J Med 1967, 277:1236–1241.
- 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, 61:332–351.
- 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. *Prim Care Respir J* 2011, 20:84–91.
- Kinnersley P, Anderson E, Parry K, Clement J, Archard L, Turton P, Stainthorpe A, Fraser A, Butler CC, Rogers C: Randomised controlled trial of nurse practitioner versus general practitioner care for patients requesting "same day" consultations in primary care. *BMJ* 2000, 320:1043–1048.
- 27. Kernick D, Powell R, Reinhold D: A pragmatic randomised controlled trial of an asthma nurse in general practice. *Prim Care Respir J* 2002, 11:6–8.
- 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. *Br J Gen Pract* 2000, **50**:555–558.
- 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: randomised controlled trial. *BMJ* 2002, **324**:1072–1075.
- Houweling ST, Kleefstra N, van Hateren KJ, Groenier KH, Meyboom-de Jong B, Bilo HJ: Can diabetes management be safely transferred to practice nurses in a primary care setting? A randomised controlled trial. J Clin Nurs 2011, 20:1264–1272.
- 31. 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. *Br J Gen Pract* 2006, **56**:530–535.
- Hiss RG, Armbruster BA, Gillard ML, McClure LA: Nurse care manager collaboration with community-based physicians providing diabetes care: a randomized controlled trial. *Diabetes Educ* 2007, 33:493–502.
- 33. Hesselink AE, Penninx BW, van der Windt DA, van Duin BJ, de Vries P, Twisk JW, Bouter LM, van Eijk JT: Effectiveness of an education programme by a general practice assistant for asthma and COPD patients: results from a randomised controlled trial. *Patient Educ Couns* 2004, 55:121–128.
- Hemani A, Rastegar DA, Hill C, al-Ibrahim MS: A comparison of resource utilization in nurse practitioners and physicians. *Eff Clin Pract* 1999, 2:258–265.
- Flynn BC: The effectiveness of nurse clinicians' service delivery. Am J Public Health 1974, 64:604–611.
- 36. Fairall L, Bachmann MO, Lombard C, Timmerman V, Uebel K, Zwarenstein M, Boulle A, Georgeu D, Colvin CJ, Lewin S, Faris G, Cornick R, Draper B, Tshabalala M, Kotze E, van Vuuren C, Steyn D, Chapman R, Bateman E: Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. *The Lancet* 2012, 380(9845):889–898.

- 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. Journal of Wound, Ostomy, & Continence Nursing 2007, 34:631–640.
- 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. Br J Gen Pract 2010, 60:28–33.
- 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, 65:391–401.
- 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, 26:2256–2260.
- Delaney EK, Murchie P, Lee AJ, Ritchie LD, Campbell NC: Secondary prevention clinics for coronary heart disease: a 10-year follow-up of a randomised controlled trial in primary care. *Heart* 2008, 94:1419–1423.
- Chan D, Harris S, Roderick P, Brown D, Patel P: A randomised controlled trial of structured nurse-led outpatient clinic follow-up for dyspeptic patients after direct access gastroscopy. BMC Gastroenterol 2009, 9:12.
- Campbell NC, Thain J, Deans HG, Ritchie LD, Rawles JM, Squair JL: Secondary prevention clinics for coronary heart disease: randomised trial of effect on health. *BMJ* 1998, 316:1434–1437.
- 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, 316:1430–1434.
- Campbell NC, Ritchie LD, Thain J, Deans HG, Rawles JM, Squair JL: Secondary prevention in coronary heart disease: a randomised trial of nurse led clinics in primary care. *Heart* 1998, 80:447–452.
- 46. 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, 16:205–214.
- Laurant MG, Hermens RP, Braspenning JC, Akkermans RP, Sibbald B, Grol RP: An overview of patients' preference for, and satisfaction with, care provided by general practitioners and nurse practitioners. J Clin Nurs 2008, 17:2690–2698.
- 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.
- Dierick-van Daele AT, Spreeuwenberg C, Derckx EW, Metsemakers JF, Vrijhoef BJ: Critical appraisal of the literature on economic evaluations of substitution of skills between professionals: a systematic literature review. J Eval Clin Pract 2008, 14:481–492.
- Buchan J, Dal Poz MR: Skill mix in the health care workforce: reviewing the evidence. Bull World Health Organ 2002, 80:575–580.

doi:10.1186/1472-6963-14-214

Cite this article as: Martínez-González *et al.*: **Substitution of physicians by nurses in primary care: a systematic review and meta-analysis.** *BMC Health Services Research* 2014 **14**:214.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

) BioMed Central

Submit your manuscript at www.biomedcentral.com/submit