Quantity, topics, methods and findings of randomised controlled trials published by German university departments of general practice – systematic review

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Abstract

Background: Academic infrastructures and networks for clinical research in primary care receive little funding in Germany. We aimed to provide an overview of the quantity, topics, methods and findings of randomised controlled trials published by German university departments of general practice.

Methods: We searched Scopus (last search done in April 2015), publication lists of institutes and references of included articles. We included randomised trials published between January 2000 and December 2014 with a first or last author affiliated with a German university department of general practice or family medicine. Risk of bias was assessed with the Cochrane tool, and study findings were quantified using standardised mean differences (SMDs).

Results: Thirty-three trials met the inclusion criteria. Seventeen were cluster-randomised trials, with a majority investigating interventions aimed at improving processes compared with usual care. Sample sizes varied between 6 and 606 clusters and 168 and 7807 participants. The most frequent methodological problem was risk of selection bias due to recruitment of individuals after randomisation of clusters. Effects of interventions over usual care were mostly small (SMD <0.3). Sixteen trials randomising individual participants addressed a variety of treatment and educational interventions. Sample sizes varied between 20 and 1620 participants. The methodological quality of the trials was highly variable. Again, effects of experimental interventions over controls were mostly small.

Conclusions: Despite limited funding, German university institutes of general practice or family medicine are increasingly performing randomised trials. Cluster-randomised trials on practice improvement are a focus, but problems with allocation concealment are frequent.

Keywords: Germany, Primary care, General practice, Randomised controlled trials, Academic performance

Background

Practice-based randomised controlled trials (RCTs) in primary care are essential, as they provide the basis for evidence-based decision-making in a central sector of health care [1]. Furthermore, being considered the gold standard for clinical research, high-quality RCTs led by general practitioners (GPs) are of crucial importance to enhance the still limited acceptance of general practice/family medicine as an academic discipline at German universities [2]. In recent years, several countries, such as the United Kingdom, the United States and the Netherlands, have invested greatly in the establishment of an efficient primary care research infrastructure (university departments of general practice or family medicine and practice networks) and the in practice-based RCTs [3–5].

Although Germany is Europe’s most populous country, its output of primary care research medicine lags far behind that of the United Kingdom and the Netherlands [3]. In 2000 only 5 of 36 German medical schools had a chair of general practice or family medicine, and by 2006 family medicine institutes or divisions had been established at 13 German universities [6]. By summer 2015,
chairs had been established at 25 of 37 medical schools. Recently, a group of researchers from German academic departments of general practice published an analysis of obstacles in clinical trials [5]. In Germany, laboratory research is regarded more highly than clinical research. The single national funding programme for clinical research is highly competitive and specialist-dominated, and it usually favours innovation rather than comparative effectiveness research. General practice as an academic discipline is still not fully implemented, and most of the existing institutes are small. German GPs work in a market-oriented competitive system, mostly in small practices with a high caseload. Sustained funding for research-oriented practice networks is almost inexistent [5]. Despite these difficult circumstances, researchers in German university departments of general practice or family medicine have performed a number of randomised trials in recent years. Our aim in this article is to provide a descriptive overview of the current status of research productivity by performing a systematic review of the amount, topics, methods, quality and findings of randomised trials carried out by German university departments of general practice.

Methods
The aims and basic methods we used to search the literature, establish the selection criteria and process, extract data, and assess risk of bias were predefined in an unpublished protocol (in German).

Literature search
Publications were identified (1) by searching the Scopus database (http://info.scopus.com; last searched 22 Apr 2015); (2) by screening publication lists of existing departments, institutes and divisions of general practice or family medicine at German medical schools; and (3) by tracking potentially relevant references in already-included articles. We selected Scopus as a database for electronic searching as it comprises PubMed/MEDLINE and also covers European journals in languages other than English, which are rarely listed in PubMed/MEDLINE. The following algorithm was used for our Scopus database search: AFFILCOUNTRY (deutschland) OR AFFILCOUNTRY (germany) AND AFFILORG (allgemeinmedizin) OR AFFILORG (general practice) AND PUBYEAR > 2009 AND PUBYEAR < 2015 AND (Random* OR Cluster). Publication lists were obtained directly from the departments, institutes and division and/or from their websites. Articles published until 2010 had been originally searched and identified for a previous review on any original research publication done by researchers at German academic family medicine departments [7, 8]. Articles published between 2011 and 2014 were identified by updated searches. (The year 2010 was also searched to detect trials potentially added to Scopus after completion of the search for our previous work.)

Study selection
We included randomised (individual- or cluster-level) controlled trials published between January 2000 and December 2014 in which the first or last author of at least one relevant publication (study protocol and/or a publication reporting trial results) was affiliated with a general practice or family medicine department, institute or division of a German medical school. (For simplicity, only the term department is used in the rest of this article.) Within the overall project, we also collected published study protocols of RCTs for which results were not yet available by the end of 2014, but these are not included in the systematic review presented here. There were no predefined further exclusion criteria.

One reviewer screened titles and (to the extent available) abstracts of all Scopus search hits and excluded all clearly irrelevant publications. The full text was obtained for all remaining articles. For our previous review project [7], these were any articles potentially reporting original data. All articles actually reporting original data were then analysed for study topic and bibliographical and methodological characteristics. For our present analyses, only articles reporting on a prospective clinical trial with a control group or a protocol of such a study were considered as potentially relevant and checked as full texts. Titles and abstracts identified by our updated searches (2010–2014) were screened for randomised trials; publications clearly not reporting or related to a randomised trial were excluded. The first author checked all full texts obtained formally for compliance with our selection criteria. In cases of uncertainties, the senior author also read and assessed the articles.

Data extraction
One reviewer extracted the following information (apart from reference information included in the Endnote file) from all included studies: study question in participants, intervention, control, outcome format; in case of a disease focus, the condition was recorded according to coding in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, and the International Classification of Primary Care, Second Edition (http://www.who.int/classifications/icd/adaptations/icpc2/en/); information on authors; type and number of participating practices; the number of patients included, analysed and completing the studies, as well as information on recruitment; funding; study design issues, including duration, randomisation, blinding, sample size calculation and analysis; relevant outcome measures; and definition of a primary outcome measure.
Assessment of risk of bias
Risk of bias was assessed using the risk of bias assessment tool of the Cochrane Collaboration [9] with items on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Assessment was performed on the basis of the instructions given in the Cochrane Handbook [9] with a ‘rule book’ further standardising procedures, taking into account the great clinical and methodological diversity of the trials included in our review. Assessments were done by the first author. About half of the assessments were checked again by the senior author.

Summarising the results of included trials
To provide a crude overview of the results of the included trials, we used both vote count methods and effect size calculations. For the vote count, the first author categorised overall study findings as ‘positive’ (findings in the intervention group consistently and statistically significantly better than in the control group), ‘trend positive’ (significant differences in favour of the intervention group only for some outcomes), ‘no difference’, ‘trend negative’ and ‘negative’ (as ‘trend positive’ and ‘positive’ but favouring the control group). Two vote counts were done: one based on what study authors reported and concluded and one according to the reviewer’s perception.

In addition, we calculated effect size estimates for predefined main outcome measures or, if a main outcome measure was not clearly defined, for the outcome we considered most relevant. Raw data in four formats (means, standard deviations and sample sizes; mean differences, samples sizes and p values or confidence intervals; events and number of participants per group; odds ratios and confidence intervals) were entered into a Comprehensive Meta-Analysis 3.3 spreadsheet (http://www.meta-analysis.com/index.php). This software allows conversion of different types of raw data into standardised mean differences (with 95% confidence intervals). Positive values indicate better outcomes in the intervention group. We considered standardised mean differences ≤0.4 as small effects, between 0.41 and 0.7 as moderate effects and >0.7 as large effects [10].

Results
In our literature searches, we identified a total of 2228 references published between January 2000 and December 2014 (Fig. 1). On the basis of our review of titles and abstracts or the full-text check of articles which had already been identified for our previous review [7], a total of 2005 references were excluded as clearly irrelevant. Altogether, full texts of 223 publications were obtained. Of these, 128 were excluded because neither the first nor the last author was associated with a GP department, the studies were not randomised trials, or the authors reported additional information related to a randomised trial included which was not directly related to the main results (e.g., accompanying qualitative studies or cross-sectional analyses of baseline data). We extracted basic information on 60 studies described in 95 publications. Twenty-seven studies in 33 publication were excluded from the review (see Additional file 1 for references and Additional file 2 for study characteristics). For 17 trials, protocols (17 publications) were published between 2008 and 2014, but results were not available at the end of 2014. We decided post hoc to exclude a further 10 trials (16
Cluster-randomised trials

The 17 cluster-randomised trials had a total of 37 study arms (14 two-armed and 3 three-armed trials; Table 2). Units of randomisation were quality circles or continuing medical education groups of several physicians in 3 studies, practices in 12 studies and individual physicians in 2 studies. Outcomes were measured on the level of individual patients in all but one study, in which the outcome was measured on the level of physicians. The number of randomised clusters varied between 6 and 303, and the number of included patients (physicians in 1 study) ranged between 168 and 7807. The conditions or clinical problems and outcomes assessed varied widely; no specific subject was investigated in more than one study. The majority of interventions were focused on the improvement of processes (managed care, more efficient or evidence-based strategies, better communication), and only a few were focused on defined, specific treatment strategies (e.g., a weight reduction program or a fall prevention intervention for the elderly). Control interventions were no intervention/usual care or minimal interventions unlikely to have relevant effects.

Many cluster-randomised trials were logistically complex and associated with high risk of bias (Table 3). While the generation of the random sequence was either adequate (ten studies) or not reported (seven studies), we considered the risk of selection bias related to allocation concealment high in ten studies, unclear in a further two and low in only five. The allocation of clusters was mostly concealed adequately. However, in those ten studies which received a high-risk rating, patients were explicitly or probably recruited after the practices knew their allocation status. Most authors seem to have been aware of this problem but were unable to manage recruitment otherwise. While in some trials this did not result in obvious imbalances, in others the number of patients recruited in the intervention and control groups differed beyond chance or there were clinically relevant differences in baseline characteristics of patients. Given the nature of the interventions tested, blinding of practices and individuals was not possible in any trial. While outcomes measured were partly objective, performance bias on the level of co-interventions cannot be ruled out. In five trials, a relevant proportion of randomised clusters did not recruit any patients and/or had a high percentage of incomplete outcome data, which resulted in a high risk of attrition bias. We considered the risk of major bias on the level of reporting outcomes to be low based on our (liberal) operationalization of this item. In summary, each of the cluster-randomised trials had a high risk of bias for at least one item.

In the vote count, the conclusions of authors were categorised as ‘positive’ for five trials, as ‘trend positive’ in three and as ‘no difference’ in nine trials. The vote count based on the reviewer’s conclusion yielded similar categorisations (four, three and ten trials, respectively). Effect sizes estimates could be calculated for 15 trials with 18 comparisons of an intervention with a control group (Table 4). Only two trials had moderately large group differences, with standardised mean differences of −0.60 and −0.63, respectively. In all other trials, differences were small, ranging from −0.30 to 0.17. Confidence intervals did not include zero in eight trials.

‘Normal’ randomised trials

In a total of 16 trials with 33 study arms (one 3-armed trial), the unit of randomisation and the level of outcome measurement were the same (Table 2). In 11 trials, researchers investigated the effectiveness of specific clinical interventions; these interventions were allocated to individual patients. Conditions as well as experimental and control interventions investigated were highly variable. Six of the eleven trials investigated complementary
Table 1 | Characteristics of included studies - cluster-randomised trials (n = 17)

| First author, year | Participants’ conditions | Interventions | Controls | Main outcomes | Unit random. | Sample size*
|---------------------|--------------------------|---------------|----------|---------------|--------------|----------------
| Altiner, 2007       | Cough                    | Educational intervention (GPs and patients) | No intervention | Antibiotic prescribing | Physician | 104/2787
| Becker, 2010        | Low back pain            | Group 1: Multifaceted guideline intervention Group 2: 1 + training of practice nurses | Postal dissemination of the guideline | Functional capacity | Practice | 118/1378
| Erler, 2012         | Elderly with chronic kidney disease | Multifaceted intervention helping adequate drug dosing | Usual care | Prescription exceeding recommended doses >30 % | Practice | 46/404
| Freiberger, 2013    | Community-dwelling elderly | Risk of falls prevention program | No intervention | Risk of falling (main outcome falls not yet available) | Practice | 33/378
| Gensichen, 2009     | Depression                | Case management (communication, monitoring, behavioural activation) | Usual care | Depressive symptoms | Practice | 74/626
| Junius-Walker, 2012 | Elderly GP patients       | Training on structured priority-setting consultation | No training | Doctor-patient agreement on priorities | Practice | 42/347
| Kaufmann-Kolle, 2011| Asthma bronchiiale       | Quality circles with open benchmark | Traditional anonymous feedback in quality circles | Inappropriate drug combinations, asthma severity | Quality circle | 6/unclear
| Krones, 2008        | All undergoing cholesterol measurement | Communication/shared decision-making in cardiovascular risk patients | Training on other subjects | Patient satisfaction, risk scores, participation | CME groups | 14/1132
| Mehring, 2013       | Individuals with BMI ≥25 kg/m² | Web-based weight reduction program | Usual care | Weight reduction at 12 weeks | Practice | 92/186
| Mehring, 2014       | Individuals willing to stop smoking | Web-based weight reduction program | Usual care | Biochemically confirmed smoking status at 12 weeks | Practice | 92/168
| Peters-Klimm, 2009  | Chronic heart failure    | Multifaceted, interdisciplinary medical educational intervention | Single 3-h lecture | Quality of life | Practice | 37/168
| Rosemann, 2007      | Osteoarthritis            | Group 1: Case management training GPs Group 2: 1 + courses also for nurses | No intervention | Quality of life (Arthritis Impact Measurement Scales Short Form) | Physician | 75/1125
| Szecsenyi, 2012     | Type 2 diabetes           | Ideally implemented disease management | Usual disease management care | Achievement of target values for HbA1c and blood pressure | Practice | 177/7807
| Tinsel, 2013        | Hypertension              | Shared decision-making training | No training (usual care) | Patients’ perceived participation, blood pressure | Practice | 37/1120
| Vollmar, 2007       | Dementia                  | Training in evidence-based dementia treatment (two slightly different groups) | Basic information (usual care) | Time to nursing home placement, death | Practice | 303/390
| Vollmar, 2010       | GPs                      | Blended learning intervention on dementia care | Lecture and case discussion | Knowledge gain | Quality circle | 26/305
| Vormfelde, 2014     | Patients receiving oral anticoagulation therapy | Educational program for patients provided by practice nurses | Brochure only | Knowledge, feelings about safety, complications | Practice | 22/345

*For cluster-randomised trials, first number of clusters randomised/number of patients

Unit random. unit of randomisation, GP general practitioner, CME continuing medical education, HbA1c haemoglobin A1c, BMI body mass index
See Additional file 1 for references
### Table 2 Characteristics of included studies: ‘normal’ randomised trials (n = 16)

| First author, year | Participants/conditions | Interventions | Controls | Main outcomes | Unit random. | Sample size |
|--------------------|-------------------------|---------------|----------|---------------|--------------|-------------|
| **Randomised trials investigating specific treatments (n = 11)** | | | | | | |
| Bleidorn, 2010  | Uncomplicated urinary tract infection | Ibuprofen | Ciprofloxacin | Symptom resolution at day 4 | Patient | 80 |
| Bücker, 2010  | Acute, uncomplicated back pain | Handing out evidence-based back pain leaflet | Non-specific information | Functional capacity (Hannover Functional Ability Questionnaire) | Patient | 189 |
| du Moulin, 2009  | COPD | Home-based exercise training | No intervention | 6-minute walk test, quality of life, lung function | Patient | 20 |
| Frese, 2012  | GP patients older than 70 years of age | Comprehensive geriatric assessment | Usual care | Mortality, nursing home admission | Patient | 1620 |
| Gastpar, 2003  | Neurotic anxiety | Kava special extract WS 1490 | Placebo | Anxiety Status Inventory | Patient | 141 |
| Hensler, 2009  | Common cold | Intramuscular autologous blood therapy | Placebo | Duration of cold | Patient | 139 |
| Jobst, 2005  | Recurrent respiratory infections | Intramuscular autologous blood injection | Homeopathic complex remedy (Engystol®, Biologische Heilmittel Heel, Baden-Baden, Germany) | Sick days | Patient | 80 |
| Klein, 2013  | Non-specific neck pain | Strain-counterstrain (osteopathic technique) | Sham intervention | Range of motion and pain intensity | Patient | 61 |
| Peters-Klimm, 2010  | Chronic heart failure | Case management (telephone monitoring and home visits) | Usual care | Quality of life, Kansas City Cardiomyopathy Questionnaire | Patient | 199 |
| Schencking, 2013  | Osteoarthritis (hip or knee) | Group 1: Kneipp hydrotherapy | Both | Pain intensity, quality of life, mobility | Patient | 30 |
| Voigt, 2011  | Migraine | Osteopathic manipulative treatment | No intervention | Migraine Disability Assessment (MIDAS), quality of life, pain | Patient | 42 |
| **Randomised trials on other topics (n = 5)** | | | | | | |
| Bergold, 2013  | First-year residents | Online course in evidence-based medicine | Wait list | Knowledge gain | First-year resident | 120 |
| Blank, 2013  | Medical students | Additional near-peer teaching for physical examination | Established curricular course only | Objective structured clinical examination | Medical student | 84 |
| Butzlaff, 2004  | General practitioners | Access to computerized guidelines | No specific access | Knowledge gain | Physician | 72 |
| Hoffmann, 2014  | Physicians and nurses of GP practices | Team-based patient safety culture assessment and intervention | Short, facilitative seminar on error management | Error management | Practice | 65 |
| Müller-Bühl, 2011  | Adult GP patients | Answering three questions before completing the SF-36 quality of life questionnaire | Completing the SF-36 as usual | Number of missing items | Patient | 215 |

COPD chronic obstructive pulmonary disease, GP general practitioner, SF-36 36-item Short Form Health Survey, Unit random. unit of randomisation
See Additional file 1 for references
or alternative treatments (e.g., herbal drugs, autologous blood therapy, osteopathy or hydrotherapy). Sample sizes varied between 20 and 1620 patients. In the five remaining trials, researchers investigated educational interventions (three trials), the impact of access to computerized guidelines (one trial) and a methodological issue relevant to quality of life measurement in heterogeneous GP patient populations (one trial). The unit of randomisation was variable. Sample sizes varied between 72 and 215 participants.

In general, ‘normal’ randomised trials were logistically and methodologically less challenging than cluster-randomised trials. While not all trials reported details on sequence generation and allocation concealment, the

| Table 3 Risk of bias |
|----------------------|
| First author, year   | Sequence generation | Allocation concealment | Blinding of participants | Blinding of outcome assessment | Incomplete outcome data | Selective reporting |
|----------------------|---------------------|------------------------|--------------------------|-------------------------------|------------------------|-------------------|
| Cluster-randomised trials |
| Altiner, 2007        | Low                 | High                   | High                     | Low                           | High                   | Low               |
| Becker, 2010         | Low                 | High                   | High                     | High                          | High                   | Low               |
| Erler, 2012          | Low                 | Low                    | High                     | Low                           | Low                    | Low               |
| Freiberg, 2013       | Low                 | Low                    | High                     | High                          | Low                    | Low               |
| Gensichen, 2009      | Low                 | High                   | High                     | High                          | Low                    | Low               |
| Junius-Walker, 2012  | Unclear             | High                   | High                     | High                          | Unclear                | Low               |
| Kaufmann-Kolle, 2011 | Unclear             | High                   | High                     | Unclear                       | High                   | Low               |
| Krones, 2008         | Unclear             | High                   | High                     | High                          | Unclear                | Low               |
| Peters-Klimm, 2009   | Low                 | Low                    | High                     | Low                           | Unclear                | Low               |
| Mehring, 2013        | Low                 | High                   | High                     | Low                           | Unclear                | Low               |
| Mehring, 2014        | Low                 | High                   | High                     | Low                           | Unclear                | Low               |
| Rosemann, 2007       | Unclear             | Low                    | High                     | High                          | Unclear                | Low               |
| Szecsenyi, 2012      | Unclear             | Unclear                | High                     | Low                           | Low                    | Low               |
| Tinsel, 2013         | Low                 | Low                    | Unclear                  | Unclear                       | Low                    | Low               |
| Vollmar, 2007        | Unclear             | High                   | High                     | Low                           | Low                    | Low               |
| Vollmar, 2010        | Unclear             | Low                    | High                     | High                          | Unclear                | Low               |
| Vormfelde, 2014      | Low                 | Unclear                | High                     | High                          | Unclear                | Low               |

Randomised trials investigating specific treatments

Bleidorn, 2010 | Low | Low | Low | Low | Low | Low | Low |
Bücke, 2010    | Low | Low | High | High | High | Low | Low |
du Moulin, 2009| Low | Low | High | Low | Unclear | Low | Low |
Frese, 2012    | Unclear | Unclear | Low | High | High | Low | Low |
Gastpar, 2003  | Low | Low | Low | Low | Low | Low | Unclear |
Hensler, 2009  | Unclear | Low | Low | Low | Unclear | Low | Low |
Jobst, 2005    | Low | Low | High | High | Unclear | Low | Low |
Klein, 2013    | Low | Low | Low | Low | Low | Low | Low |
Peters-Klimm, 2010| Low | Low | High | High | Unclear | High | Low |
Schencking, 2013| Low | Low | High | High | Unclear | Low | Unclear |
Voigt, 2011    | Unclear | Unclear | High | High | Low | High | High |

Randomised trials on other topics

Bergold, 2013  | Low | Low | High | High | Low | Low | Low |
Blank, 2013    | Low | Low | High | High | Low | Low | Low |
Butzlaff, 2004 | Low | Unclear | High | High | Low | Low | Low |
Hoffmann, 2014 | Unclear | Unclear | Low | Low | Low | Low | Low |
Müller-Bühl, 2011| Unclear | Unclear | Unclear | Low | Low | Low | Low |

See Additional file 1 for references.
risk of bias was never considered high. Instead, the risk of performance and measurement bias was considered high in the majority of studies due to the lack of blinding and/or use of subjective outcomes. Risk of bias due to incomplete outcome data was highly variable due to differences in challenges (some short-term studies did not have any attrition and had no or little missing data) and reporting or handling of the problems experienced. In two trials, there was clear evidence of biased reporting, either by selecting outcomes or by reporting inadequate

| First author, year | Outcome used for effect size estimation | SMD | LL  | UL  |
|--------------------|----------------------------------------|-----|-----|-----|
| **Cluster-randomised trials** |                                        |     |     |     |
| Altiner, 2007      | Frequency of antibiotic prescription   | 0.30| 0.14| 0.46|
| Becker, 2010       | Functional capacity 6 (group 1 vs. controls) | 0.15| 0.01| 0.29|
| Becker, 2010       | Functional capacity 6 (group 2 vs. controls) | 0.11| −0.03| 0.25|
| Erler, 2012        | Number of patients with inadequate prescriptions | 0.23| −0.11| 0.56|
| Gensichen, 2009    | Depression scores                      | 0.22| 0.05| 0.38|
| Krones, 2008       | Patient participation and satisfaction score | 0.23| 0.10| 0.35|
| Peters-Klimm, 2009 | Quality of life physical function      | −0.17| −0.50| 0.16|
| Rosemann, 2007     | Arthritis impact, lower body (group 1 vs. controls) | 0.08| −0.09| 0.25|
| Rosemann, 2007     | Arthritis impact, lower body (group 2 vs. controls) | 0.17| 0.00| 0.34|
| Szecsenyi, 2012    | Number of patients reaching treatment targets | 0.01| −0.04| 0.07|
| Tinsel, 2013       | Shared decision-making score           | 0.07| −0.06| 0.20|
| Vollmar, 2007      | Institutionalisation (group 1 vs. controls) | 0.08| −0.24| 0.41|
| Vollmar, 2007      | Institutionalisation (group 2 vs. controls) | −0.07| −0.38| 0.25|
| Vormfelde, 2014    | Knowledge scores anticoagulant treatment | 0.63| 0.41| 0.85|
| Freiberger, 2013   | Mobility                               | 0.27| 0.05| 0.49|
| Mehring, 2013      | Weight reduction                       | 0.60| 0.27| 0.92|
| Mehring, 2014      | Smoking cessation                       | 0.08| −0.61| 0.77|
| Vollmar, 2010      | Knowledge gain                          | 0.02| −0.28| 0.33|
| **Randomised trials investigating specific treatments** |                                        |     |     |     |
| Bücker, 2010       | Functional capacity                     | 0.28| −0.10| 0.66|
| Peters-Klimm, 2010 | Quality of life physical functioning    | −0.04| −0.38| 0.31|
| Bleidorn, 2010a    | No symptom resolution                   | 0.15| −0.37| 0.68|
| du Moulin, 2009    | 6-minute walk test                      | 1.03| 0.10| 1.97|
| Frese, 2012        | Death                                  | 0.14| 0.05| 0.22|
| Gastpar, 2003      | Anxiety scores                          | 0.15| −0.18| 0.48|
| Hensler, 2009      | Illness duration                        | 0.05| −0.32| 0.41|
| Jobst, 2005a       | Illness days                            | 0.02| −0.42| 0.46|
| Klein, 2013        | Mobility restriction, neck              | 0.24| −0.27| 0.74|
| Schencking, 2013   | Pain (group 1 vs. controls)             | 0.20| −0.68| 1.08|
| Schencking, 2013   | Pain (group 2 vs. controls)             | 0.10| −0.78| 0.97|
| **Randomised trials on other topics** |                                        |     |     |     |
| Bergold, 2013      | Knowledge of EBM                        | 0.76| 0.38| 1.14|
| Blank, 2013        | Score for clinical examination quality  | 1.16| 0.58| 1.74|
| Butzlaff, 2004     | Knowledge gain                          | 0.11| −0.43| 0.65|
| Hoffmann, 2014     | Error management                        | −0.06| −0.57| 0.45|
| Müller-Bühl, 2011  | Number of missing items                 | 0.25| −0.02| 0.52|

SMD standardised mean difference, LL lower limit of the 95 % confidence interval, UL upper limit of the 95 % confidence interval

*Studies comparing two active treatments (equivalence or non-inferiority trials)

Data are presented as standardised mean differences with 95 % confidence intervals. Negative values indicate better outcomes in the intervention group.

See Additional file 1 for references
analyses (focus on changes and inference testing within groups).

The authors’ conclusions were ‘positive’ in four trials, ‘trend positive’ in six and ‘no difference’ in six trials (reviewer’s conclusion three trials ‘positive’, five trials ‘trend positive’ and eight trials ‘no difference’). Standardised mean differences could be calculated for 15 trials including 16 comparisons (Table 4, lower part). Two trials actually compared active treatments. Large differences were reported in two trials and moderately large differences in one trial. In all other trials, point estimates of standardised mean differences were <0.3.

Discussion
Despite limited funding, German university institutes for general practice or family medicine increasingly perform randomised trials; yet, the total number of 33 trials relevant to primary care published in a period of 15 years seems modest. In cluster-randomised trials, we noticed an emphasis on interventions aimed at improving processes in practices, while trials on drugs were very rare. The methodological quality of the trials was variable, with frequent relevant problems related to allocation concealment in cluster-randomised trials. Effects of the tested interventions over usual care or minimal interventions were mostly small.

It is somewhat difficult to compare the RCT output of university departments for general practice in Germany with that of other countries, as there is very limited information on such output internationally. The only systematic analysis limited to ‘RCTs with a general practice setting’ we found in the literature was published by Kortekaas et al. in 2012 [2]. These authors searched MEDLINE using the text words and/or MeSH (‘medical subject headings’) terms ‘general practice’, ‘primary healthcare’ or ‘family medicine’ to identify relevant trials published between 1990 and 2010. The 1935 publications on RCTs included 549 originated from the United States, 511 from the United Kingdom, 201 from Scandinavia, 194 from the Netherlands and 480 from a variety of other countries. The number of trials originating from Germany was not reported in the published review, but the first author kindly provided us an unpublished list of the 52 German studies. Of the 38 publications included by Kortekaas et al. that were published between 2000 and 2010, 8 were also included by us (while we identified additional 9 trials for this period), 3 were relevant protocol publications without results (also identified by us but excluded from the analysis presented), 1 was an additional publication on a trial already included in both reviews, 1 turned out not to be a randomised trial and 1 publication was a duplicate. The remaining 24 publications were not included by us because in 22 not a single author was affiliated with a GP department (or at least reported a private general practice as contact) and in 2 only a middle author had a GP department affiliation. This comparison shows that, depending on the objective and the methods used, bibliometric analyses can produce quite different findings. Yet, it makes clear that, compared with countries leading in primary care research (UK, USA, Netherlands, Scandinavian countries), Germany’s output of RCTs in the area of academic family medicine is rather low, and that many ‘primary care trials’ in Germany are conducted with or on GPs rather than by GPs.

There is a remarkable focus by German GP institutes on process-oriented cluster-randomised trials. Also, among the 16 protocols of trials without published results by 2014 identified by our search, 12 described cluster-randomised trials (see Additional file 2). This focus seems well compatible with the priorities in the research agenda of the European General Practice Research Network that ask for RCTs ‘which take into account broad issues such as patient preferences, multimorbidity, quality of life and social and environmental circumstances’ ([11] p. 11). Also, when we screened systematic reviews with the term primary care in the title in the Cochrane library (http://www.cochranelibrary.com/), it became clear that primary care research is focused more on complex and process interventions than on single specific interventions such as a defined drug. The methodological problems with allocation concealment and attrition observed in completed German cluster-randomised trials fit very well with the problems described in analyses of such trials in general [12–15]. It seems to us that the protocols of the partly very large newly planned or ongoing trials try to take these problems and former experiences into account. We are not aware of any systematic analyses of effect sizes in general practice trials across conditions, but it seems plausible to us that, in the primary care setting with its multiple influence factors, intervention effects are often small. Yet, for some of the interventions tested in the trials reviewed by us, we wondered whether these were conceptually really promising and/or well implemented.

When interpreting our findings, it must be kept in mind that we searched and included only trials in which the first or last authors were affiliated with a German university GP department. Therefore, our results cannot be adopted for RCTs authored by GPs without such an affiliation. However, our check of the additional publications identified by Kortekaas et al. [2] suggests the number of such studies is small. We excluded ten trials post hoc as they either were conducted when authors were working at other departments (and only written up later) or had no thematic relation to primary care whatsoever. We think these exclusions were necessary to allow for a judgement of the real RCT output of German academic GP departments relevant for their field. Due to limited
resources, many working steps in this review were performed by a single author, with only some checks done by a second author. Therefore, some extraction or assessment errors might have gone undetected. The standardised mean differences calculated by us should be interpreted only as crude indicators of how large differences between groups were and should not be used for clinical decision-making.

Conclusions

Researchers in Germany’s academic departments of general practice and family medicine increasingly perform and publish RCTs. However, without increased and sustained funding for research infrastructure and single trial projects, there will be little chance to catch up with leading countries such as the United Kingdom, the Netherlands, Scandinavian countries or the United States. We hope that our analysis will help to avoid some preventable shortcomings in future trials.

Additional files

Additional file 1: References of included and excluded trials. (DOCX 32 kb)
Additional file 2: Details of excluded studies. (DOCX 17 kb)

Abbreviations

BMI: body mass index; CME: continuing medical education; COPD: chronic obstructive pulmonary disease; EBM: evidence-based medicine; GP: general practitioner; HbA1c: haemoglobin A1c; LL: lower limit of the 95 % confidence interval; RCT: randomised controlled trial; SF-36: 36-item Short Form Health Survey; SMD: standardised mean difference; UL: upper limit of the 95 % confidence interval.

Competing interests

AS and KL were involved in several of the trials reviewed. SH declares that he has no competing interests.

Authors’ contributions

SH, AS, and KL were involved with study planning and interpretation and revision of manuscript drafts. SH performed the literature search, study selection, data extraction, risk of bias assessment, data entry, and vote counts. KL performed checks of data extraction and risk of bias assessments, extraction and calculation of effect size measures, and drafting of the manuscript. All authors read and approved the final manuscript.

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