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RESEARCH

Radial extracorporeal shockwave treatment compared with supervised exercises in patients with subacromial pain syndrome: single blind randomised study

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ABSTRACT

Objective To compare the effectiveness of radial extracorporeal shockwave treatment with that of supervised exercises in patients with shoulder pain.

Design Single blind randomised study.

Setting Outpatient clinic of physical medicine and rehabilitation department in Oslo, Norway.

Participants 104 patients with subacromial shoulder pain lasting at least three months.

Interventions Radial extracorporeal shockwave treatment: one session weekly for four to six weeks. Supervised exercises: two 45 minute sessions weekly for up to 12 weeks.

Primary outcome measure Shoulder pain and disability index.

Results A treatment effect in favour of supervised exercises at 6, 12, and 18 weeks was found. The adjusted treatment effect was −8.4 (95% confidence interval −16.5 to −0.6) points. A significantly higher proportion of patients in the group treated with supervised exercises improved—odds ratio 3.2 (1.3 to 7.8). More patients in the shockwave treatment group had additional treatment between 12 and 18 weeks—odds ratio 5.5 (1.3 to 26.4).

Conclusion Supervised exercises were more effective than radial extracorporeal shockwave treatment for short term improvement in patients with subacromial shoulder pain.

Trial registration Clinical trials NCT00653081.

INTRODUCTION

Patients with subacromial shoulder pain are often treated with physiotherapy, non-steroidal anti-inflammatory drugs, and corticosteroid injections. Physiotherapy includes a variety of modalities such as electrotherapy, radial extracorporeal shockwave treatment, ultrasound treatment, laser treatment, manual therapy, supervised exercises, sling exercise treatment, and acupuncture.[1-4] Some evidence exists for the effectiveness of corticosteroid injections, non-steroidal anti-inflammatory drugs, and exercises for chronic shoulder pain.[5-7] A recent systematic review concluded that surgery and exercises are equally effective for rotator cuff disease.[8]

In a systematic review, Harniman et al found moderate evidence that low energy radial extracorporeal shockwave treatment was not effective for non-calcifying rotator cuff tendinosis.[3] Additional studies including patients with calcifying or non-calcifying tendinosis reported no treatment effect compared with sham or control.[9 10] Despite these findings, shockwave treatment is increasingly used for subacromial shoulder pain. The purpose of this study was to compare the short term effect of radial extracorporeal shockwave treatment and supervised exercises in patients with subacromial shoulder pain.

METHODS

Participants and randomisation

We did a randomised single blind clinical study. Participants were recruited by physicians at a physical medicine outpatient clinic in Oslo, Norway, between July 2006 and August 2007. Women and men aged between 18 and 70 years with subacromial shoulder pain lasting at least three months were eligible for inclusion. We randomly allocated patients to treatment groups. Randomisation was stratified by sex.

Outcomes

The participants completed a comprehensive questionnaire. The main outcome measure was the shoulder pain and disability index (SPADI), a self report questionnaire. The questionnaire consists of two domains: pain (five items) and disability (eight items).[11] The total score ranges from 0 to 100 points, with a higher score indicating worse shoulder pain and disability.[11]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Supervised exercises and arthroscopic surgery are better than placebo treatment for shoulder pain

Moderate evidence suggests that low energy radial extracorporeal shockwave treatment is not effective for non-calcifying rotator cuff tendinosis

WHAT THIS STUDY ADDS

Supervised exercises are better than radial extracorporeal shockwave treatment for short term improvement in patients with subacromial shoulder pain

More patients treated with supervised exercises returned to work

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Intensity of pain during rest and activity in the previous week was measured on a nine point Likert-type scale.[12] Active range of motion was measured bilaterally.[12 13] Participants reported work status and use of drug treatment.

Follow-up

At six weeks the patients completed a questionnaire including the outcome measures. The 12 week and 18 week follow-ups were done at the hospital. A blinded physiotherapist made all the baseline and follow-up measurements.

Interventions

Both treatments were given at the clinic. The supervised exercise regimen was provided by two physiotherapists. Patients attended two 45 minute sessions weekly for a maximum of 12 weeks. Initially, the principal focus was on relearning of normal movement patterns, which could then be transferred to daily activities.[2] The initial aim was to unload the stress on the rotator cuff and subacromial structures.[2] Once dysfunctional neuromuscular patterns were normalised, endurance exercises were performed with gradually increasing resistance. Patients had an adjusted programme at home, which consisted of correction of alignment during daily living and simple low loaded exercises.

Radial extracorporeal shockwave treatment was provided by an experienced physiotherapist. The treatment was administered once a week for four to six weeks; three to five tender points were treated each time. Radial extracorporeal shockwave treatment uses low to medium energy shockwaves generated when a projectile is accelerated by compressed air and hits an applicator.[4] These impulses are delivered into the tissue and spread as spherical "radial" waves. Patients were informed that the suggested mechanism for pain relief was hyperstimulation analgesia and increased neovascularisation that improves regeneration of tissue.[3 14]

All the patients were asked not to have any additional treatment except analgesics (including anti-inflammatory drugs) for their shoulder pain for the time between the start of treatment and the 18 week follow-up.

Statistical analyses

To evaluate the treatment effect (the mean difference between the groups at six, 12, and 18 weeks), we used mixed model analysis.[15] This model includes the interaction between treatment and elapsed time, and baseline values are adjusted.[15] We estimated the smallest detectable real difference between two measurements on the same person to be 19.6 points on the shoulder pain and disability index and used this as a cut-off point.[16] We calculated the number needed to treat. We used regression with adjustment for baseline values to compare work status and drug treatment. We analysed data according to the intention to treat principle.

Table 1 | Mean (SD) scores and differences in improvement with overall P values at 18 weeks, from mixed models linear (repeated measures analysis)

	Supervised exercises	Radial extracorporeal shockwave treatment	Treatment effect (95% CI)	P value
Shoulder pain and disability index				
Baseline	48.8 (20.6)	45.1 (22.1)		
6 weeks	25.8 (21.5)	33.5 (23.3)	−10 (−17.6 to −2.3)	
12 weeks	27 (24.2)	36.1 (28.4)	−10.3 (−19.8 to −0.8)	
18 weeks	24.5 (25.6)	29.2 (25.9)	−8.4 (−16.5 to −0.6)	0.047
Pain				
At rest:				
Baseline	3.4 (1.9)	3.5 (2.1)		
6 weeks	2.6 (1.9)	2.9 (2.1)	−0.3 (−0.9 to 0.4)	
12 weeks	2.5 (1.8)	2.9 (2.1)	−0.3 (−0.9 to 0.3)	
18 weeks	2.5 (1.9)	2.7 (2.0)	−0.2 (−0.7 to 0.3)	0.83
During activity:				
Baseline	5.6 (2.0)	5.4 (1.9)		
6 weeks	3.9 (2.0)	4.6 (2.4)	−0.7 (−1.6 to 0.1)	
12 weeks	3.7 (2.2)	4.1 (2.4)	−0.5 (−1.3 to 0.4)	
18 weeks	3.6 (2.3)	4.1 (2.5)	−0.6 (−1.3 to 0.2)	0.42
Function				
Carrying bag:				
Baseline	4.1 (1.8)	3.6 (2.0)		
6 weeks	3.0 (1.8)	3.1 (2.1)	−0.5 (−1.1 to 0.2)	
12 weeks	3.0 (1.9)	3.2 (2..0)	−0.4 (−1.0 to 0.2)	
18 weeks	2.8 (1.8)	3.0 (2.1)	−0.5 (−1.0 to 0.1)	0.26
Taking down from cupboard:				
Baseline	4.9 (1.2)	4.6 (1.8)		
6 weeks	3.4 (1.7)	3.9 (1.9)	−0.7 (−1.3 to −0.01)	
12 weeks	3.1 (1.9)	3.5 (2.0)	−0.5 (−1.2 to 0.2)	
18 weeks	3.2 (1.8)	3.4 (2.0)	−0.5 (−1.1 to 0.1)	0.2

RESULTS

A total of 141 patients were eligible for inclusion, and 104 were randomised for study intervention. The groups were similar at baseline with regard to age, education, dominant arm affected, duration of pain, sick leave, shoulder pain and disability index score, and secondary outcome variables (tables 1 and 2).

Patients treated with radial extracorporeal shockwaves (n=52) received a median of five (interquartile range 4-6) treatments. Patients in the supervised exercise group (n=51) received a median of 14 (11-16) treatments. Thirteen patients in the radial extracorporeal shockwave group and three patients in the supervised exercise group received additional treatment between 12 and 18 weeks (odds ratio 5.5, 95% confidence interval 1.3 to 26.4; P=0.014).

Primary outcome

The treatment effect was in favour of supervised exercises at six, 12, and 18 weeks. At 18 weeks the treatment effect was −8.4 (95% confidence interval −16.5 to −0.6; P=0.047) points (table 1). The treatment effect was consistent when adjusted for sex (P=0.049). Thirty two out of 50 (64%) patients treated with supervised exercises and 18/50 (36%) patients treated with radial extracorporeal shockwaves achieved a reduction in shoulder pain and disability index score exceeding the smallest detectable difference of 19.6 points (odds ratio 3.2, 1.3 to 7.8; P=0.009). The number needed to treat was 3.2 (95% confidence interval 2.1 to 7.1).

Table 2 | Work status and drug treatment. Values are numbers (percentages) unless stated otherwise

Outcome	Supervised exercises	Radial extracorporeal shockwave treatment	P value
Working*:			
Baseline	31/52 (60)	26/52 (50)	
12 weeks	32/50 (64)	28/52 (54)	0.6
18 weeks	38/50 (76)	26/50 (52)	0.016
Drug treatment† (daily/each week):			
Baseline	26/52 (50)	23/52 (44)	
18 weeks	18/50 (36)	22/50 (44)	0.26

*Old age pension not included (four in supervised exercise group and two in radial extracorporeal shockwave group at all follow-ups).
†Includes drug treatments for pain, sleep problems, and depression.

Secondary outcomes

At 18 weeks, results for pain, function, and active range of motion were not statistically significant (table 1). More patients in the supervised exercise group returned to work (P=0.016) (table 2). Six patients in the supervised exercise group and one in the radial extracorporeal shockwave group used less drug treatment (table 2).

DISCUSSION

We found a small but statistically significant difference in favour of supervised exercises over radial extracorporeal shockwave treatment for the primary outcome (shoulder pain and disability index) at six, 12, and 18 weeks in patients with subacromial shoulder pain. In addition, more patients from the radial extracorporeal shockwave group (13 *v* 3) had additional treatment after 12 weeks, suggesting that they were less satisfied. The results for the differences in secondary outcomes were in favour of exercises, but differences were not significant except for change in work status after 18 weeks, which may indicate that supervised exercise is a more comprehensive rehabilitation intervention.

Strengths and limitations

The advantages of this study are the randomised design, stratification by sex, treatments provided by physiotherapists experienced in the use of the methods, high compliance, blinded observer, large number of patients attending follow-up, and intention to treat analysis. At least two possible limitations must be taken into account when interpreting the results. Firstly, we did not include a placebo group and cannot exclude the possibility that the observed results reflect a placebo effect or the natural course of the condition. Secondly, local anaesthetics were not injected into the subacromial space to improve diagnostic accuracy.

Comparison with existing literature

Our results are in agreement with results from previous trials recommending exercise therapy[6-8 17] and do not strengthen the evidence for extracorporeal shockwave treatment.[3 4 9 10 18] By using the smallest detectable real difference for an individual patient of 19.6 points as a cut-off point, we found that a larger proportion of patients in the supervised exercise group than in the radial extracorporeal shockwave treatment group improved.[16] This suggests that more patients receiving supervised exercises had clinically relevant improvement.[16 19] The number needed to treat to benefit from supervised exercises was three, which is considered clinically important.[20] However, the estimate of number needed to treat has to be interpreted with caution because of possible differences in the study population recruited from a university hospital and the population in primary care to which we wish to extrapolate. The observed improvements were largest at six weeks, suggesting that a reduction of mechanical subacromial stress and normalisation of movement patterns had occurred within a relatively short treatment period.

Conclusions

After 18 weeks, supervised exercises were better than radial extracorporeal shockwave treatment in terms of the primary outcome variable—the shoulder pain and disability index—and one secondary outcome variable—work status. We found no significant differences for the other secondary outcome variables of pain, function, active range of motion, and use of drug treatment. More patients in the supervised exercise group improved, probably owing to a treatment effect.

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1 Green S, Buchbinder R, Glazier R, Forbes A. Systematic review of randomised controlled trials of interventions for painful shoulder: selection criteria, outcome assessment, and efficacy. *BMJ* 1998;316:354-60.
2 Bohmer A, Staff PH, Brox JI. Supervised exercises in relation to rotator cuff disease (impingement syndrome, stages 1 and II): a treatment regimen and its rationale. *Physiother Theory Pract* 1998;14:93-105.
3 Harniman E, Carette S, Kennedy C, Beaton D. Extracorporeal shock wave therapy for calcific and noncalcific tendonitis of the rotator cuff: a systematic review. *J Hand Ther* 2004;17:132-51.
4 Cacchio A, Paoloni M, Barile A, Don R, de Paulis F, Calvisi V, et al. Effectiveness of radial shock-wave therapy for calcific tendinitis of the shoulder: single-blind, randomized clinical study. *Phys Ther* 2006;86:672-82.
5 Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev* 2003;(1):CD004016.
6 Hay EM, Thomas E, Paterson SM, Dziedzic K, Croft PR. A pragmatic randomised controlled trial of local corticosteroid injection and physiotherapy for the treatment of new episodes of unilateral shoulder pain in primary care. *Ann Rheum Dis* 2003;62:394-9.
7 Lombardi I Jr, Magri AG, Fleury AM, Da Silva AC, Natour J. Progressive resistance training in patients with shoulder impingement syndrome: a randomized controlled trial. *Arthritis Rheum* 2008;59:615-22.
8 Coghlan JA, Buchbinder R, Green S, Johnston RV, Bell SN. Surgery for rotator cuff disease. *Cochrane Database Syst Rev* 2008;(1):CD005619.
9 Speed CA, Richards C, Nichols D, Burnet S, Wies JT, Humphreys H, et al. Extracorporeal shock-wave therapy for tendinitis of the rotator cuff. *J Bone Joint Surg Br* 2002;84:509-12.
10 Schmitt J, Haake M, Tosch A, Hildebrand R, Deike B, Griss P. Low-energy extracorporeal shock-wave treatment (ESWT) for tendinitis of the supraspinatus: a prospective, randomised study. *J Bone Joint Surg Br* 2001;83:873-6.
11 Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. *Arthritis Care Res* 1991;4:143-9.
12 Brox JI, Staff PH, Ljunggren AE, Brevik JI. Arthroscopic surgery compared with supervised exercises in patients with rotator cuff disease (stage II impingement syndrome). *BMJ* 1993;307:899-903.
13 Triffitt PD, Wildin C, Hajioff D. The reproducibility of measurement of shoulder movement. *Acta Orthop Scand* 1999;70:322-4.

14 Gerdesmeyer L, Gollwitzer H, Diehl P, Wagner K. Radial extracorporeal shockwave therapy (rESWT) in orthopaedics. *J Miner Stoffwechs* 2004;11:36-9.
15 Fitzmaurice GM. *Applied longitudinal analysis*. Hoboken, NJ: Wiley-Interscience, 2004.
16 Ekeberg OM, Bautz-Holter E, Tveita EK, Keller A, Juel NG, Brox JI. Agreement, reliability and validity in 3 shoulder questionnaires in patients with rotator cuff disease. *BMC Musculoskelet Disord* 2008;9:68.
17 Green S, Buchbinder R, Hetrick S. Physiotherapy interventions for shoulder pain. *Cochrane Database Syst Rev* 2003;(2):CD004258.
18 Gerdesmeyer L, Wagenpfeil S, Haake M, Maier M, Loew M, Wortler K, et al. Extracorporeal shock wave therapy for the treatment of chronic calcifying tendonitis of the rotator cuff: a randomized controlled trial. *JAMA* 2003;290:2573-80.
19 De Vet HC, Ostelo R, Terwee C, van der Roer N, Knol D, Beckerman H, et al. Minimally important change determined by a visual method integrating an anchor-based and a distribution-based approach. *Qual Life Res* 2007;16:131-42.
20 Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ* 1998;316:690-3.

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Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study

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ABSTRACT

Objective To examine the use of qualitative approaches alongside randomised trials of complex healthcare interventions.

Design Review of randomised controlled trials of interventions to change professional practice or the organisation of care.

Data sources Systematic sample of 100 trials published in English from the register of the Cochrane Effective Practice and Organisation of Care Review Group.

Methods Published and unpublished qualitative studies linked to the randomised controlled trials were identified through database searches and contact with authors. Data were extracted from each study by two reviewers using a standard form. We extracted data describing the randomised controlled trials and qualitative studies, the quality of these studies, and how, if at all, the qualitative and quantitative findings were combined. A narrative synthesis of the findings was done.

Results 30 of the 100 trials had associated qualitative work and 19 of these were published studies. 14 qualitative studies were done before the trial, nine during the trial, and four after the trial. 13 studies reported an explicit theoretical basis and 11 specified their methodological approach. Approaches to sampling and data analysis were poorly described. For most cases (n=20) we found no indication of integration of qualitative and quantitative findings at the level of either analysis or interpretation. The quality of the qualitative studies was highly variable.

Conclusions Qualitative studies alongside randomised controlled trials remain uncommon, even where relatively complex interventions are being evaluated. Most of the qualitative studies were carried out before or during the trials with few studies used to explain trial results. The findings of the qualitative studies seemed to be poorly integrated with those of the trials and often had major methodological shortcomings.

INTRODUCTION

Qualitative approaches can contribute to the development and evaluation of complex and other health interventions (see bmj.com) and, increasingly, qualitative components are being included in randomised controlled trials of such interventions.[1 2] Multiple, integrated approaches may be particularly useful in the evaluation of the effects of complex health and social care interventions as these involve social or behavioural processes that are difficult to explore or capture using quantitative methods alone.[3]

We systematically examined the use of qualitative approaches alongside randomised controlled trials of complex healthcare interventions. We also explored how trial teams could improve the quality of qualitative studies linked to randomised controlled trials and how synergies between qualitative approaches and the trials can be maximised.

METHODS

From a list of randomised controlled trials published in English during 2001-3 and included in the register of the Cochrane Effective Practice and Organisation of Care Review Group[4] we sampled every fifth study for each year to obtain a sample of 100 trials.

We attempted to identify all published and unpublished qualitative studies—defined as those using

WHAT IS ALREADY KNOWN ON THIS TOPIC

Complex healthcare interventions involve social processes that can be difficult to explore using quantitative methods alone
Qualitative research can support the design of interventions and improve understanding of the mechanisms and effects of complex healthcare interventions
Increasing numbers of randomised trials of complex interventions are now thought to include qualitative components

WHAT THIS STUDY ADDS

Qualitative studies remain relatively uncommon alongside trials of complex healthcare interventions
Most of the qualitative studies identified were carried out before the trial so opportunities to understand better the effects of interventions and how they are experienced by recipients are not being fully utilised
Most of the qualitative studies had important methodological shortcomings and their findings were often poorly integrated with those of the trial in which they were nested

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qualitative methods for data collection or analysis—linked to the randomised controlled trials. We checked the primary trial for citations of qualitative studies and then located the trial in PubMed and searched for related studies and other studies published by the trials' authors. We also located the randomised controlled trial in the Science and Social Science Citation Index and checked the list of studies citing the paper. Any potentially relevant titles and abstracts were examined and full papers obtained where necessary. Finally, we contacted authors for information on published or unpublished qualitative studies linked to their trials. We received responses for 76 of the 100 papers.

Two reviewers used a standard form to extract data on each randomised controlled trial and any qualitative studies, such as descriptions and the quality of the trials and studies and information on the approaches used to combine the findings of the trials and studies. The quality of the trials was assessed using the Cochrane Effective Practice and Organisation of Care Review Group's checklist.[5] The quality of the studies was assessed using a modified checklist from the critical appraisal skills programme.[6] These modifications included further details on whether the qualitative approach was justified and appropriate to the research question, whether the research context was described adequately, and items to differentiate adequate reporting of methods from the appropriateness of those methods, in relation to the research question.

RESULTS

Thirty of the 100 trials included qualitative work. Nineteen of these qualitative studies were published. In 23 (77%) of the 30 cases the researchers employed qualitative methods for data collection and analysis. In the remaining seven cases some form of qualitative data collection was used, but no formal analysis of these data using qualitative approaches was reported. Most of the qualitative studies (n=25) were carried out before or during the randomised controlled trial (see bmj.com). An explicit theoretical basis for the intervention was reported in 12 of the 30 cases.

The 30 trials that included qualitative research were carried out in a variety of settings: 24 were carried out in primary care and the remainder evaluated interventions in secondary care or across a mix of levels. The trials, all carried out in high income countries, dealt with a wide range of healthcare issues. The methodological quality of the trials with qualitative studies was similar to those without such studies.

The objectives of the qualitative studies varied widely (see bmj.com). The 16 studies done before the trial, or before and during the trial, had one or more objectives: to explore the knowledge, attitudes, or practices of the target groups about the topic in question; to explore the illness experience of consumers; to develop the intervention; and to develop the instrument used to measure the effects of the intervention in the randomised controlled trial.

The nine qualitative studies done during the trials had a wide range of objectives. These included describing the intervention as delivered and exploring issues influencing the effects of the intervention, the illness experience of consumers, participants' experiences of the intervention (see bmj.com), and reasons for refusal to participate in the trial (see bmj.com).

Of the four qualitative studies carried out after the trial, two explored participants' experiences of the intervention, one explored factors influencing the effects of the intervention (see bmj.com), and one analysed the process for development of the intervention.

Methodological approach, sampling, data collection, and data analysis

The methodological approaches of the qualitative studies were heterogeneous. Whereas 19 did not refer to any specific approach, 11 mentioned grounded theory, ethnography, action research, or narrative approaches. Ten studies used several methods for data collection, 10 utilised individual interviews, five used focus groups, and two used different forms of observation. We were unable to obtain further information from the authors of the remaining three, unpublished, studies.

A number of studies inadequately reported several aspects of the methods—13 did not describe their sampling approach and the remainder used a mix of purposive, convenience, and random sampling. In 14 studies we could find no information on data analysis. Where methods were reported, thematic or content analysis or framework analysis (n=10) or a grounded theory approach (n=2) were utilised. Four studies used other approaches.

Links between qualitative studies and randomised controlled trials

Where the findings of the trial and qualitative studies were reported in separate papers, the link between the two was not always clear from the papers. Sixteen of the studies shared authors with the randomised controlled trial. Only nine papers explicitly described linkage between the study teams. In two of the studies the researchers stated that they had used a "mixed method" approach.

Quality of the qualitative studies

Ten qualitative studies (including the seven with no formal analysis of qualitative data) had insufficient data to allow assessment of methodological quality. The quality of the remaining 20 studies (see bmj.com) was highly variable. The most common weaknesses were lack of a clear justification for the qualitative approach used; inadequate descriptions of context, sampling, data collection, and analysis; little reflection on the researcher's role in the research process; lack of clarity on how ethical issues had been taken into consideration; and insufficient evidence to support the claims made in the study.

DISCUSSION

Qualitative studies undertaken alongside randomised controlled trials of interventions to change organisation and practice remain uncommon. Less than one third of recently completed trials of relatively complex interventions in the Cochrane Effective Practice and

Organisation of Care register included some form of qualitative research. Of these, only about two thirds were published studies. This is surprising given the nature of these interventions and the growing awareness of the role that qualitative research can play in the design and evaluation of interventions.[2 7-9] Furthermore, contacts with authors suggested that many valued the findings of qualitative studies. Constraints on resources and poor access to relevant expertise were mentioned by authors in response to our requests for information on qualitative studies. It has also been suggested that linear models for evaluating interventions may impede the use of qualitative approaches. These models, it is suggested, view such evaluation as passing through a series of phases from the development of hypotheses to efficacy trials and then effectiveness trials. This may contribute to the view that earlier phases of research do not need to incorporate qualitative studies to explore the effects of contextual and other moderating factors.[10]

Although much has been written on qualitative process evaluation alongside trials of complex interventions, the largest group of qualitative studies identified were those carried out before trials. This suggests that reviewers who aim to understand better the effects of interventions through examining qualitative process evaluations may find little data.

We identified major shortcomings in many of the studies, particularly regarding sampling, analysis, and critical analysis of the researchers' roles. Interestingly an explicit theoretical basis for the intervention was reported in over a third of cases—a higher proportion than reported in recent reviews on theory in implementation research.[11 12] Twice as many of the trials that included qualitative work also had a clearly specified theoretical basis (40%) compared with randomised controlled trials without any such work (20%). However, the use of theory is by no means the norm in studies in this specialty and it remains unclear whether interventions based explicitly on a theoretical approach are more likely to be effective than those designed using pragmatic processes.[13-15]

We found little evidence of explicit integration of data from qualitative studies and randomised controlled trials and few cases discussed mixed methods approaches.

Limitations of the study

We may not have identified all qualitative studies linked to the index randomised controlled trials. However we did receive a high response rate from the authors of the trials, and other reviews have indicated that this approach identifies the largest number of additional studies.[12] All methods of identifying studies were resource intensive—a potential barrier to examining qualitative work done alongside trials. Secondly, trials sampled from the Cochrane Effective Practice and Organisation of Care database may not be representative of those evaluating interventions to change professional practice and the organisation of care. The sampled trials are unlikely to be representative of randomised controlled trials more widely but are likely to be similar, in terms of their use of qualitative methods, to other randomised controlled trials of complex interventions. Finally, our analysis is based largely on study reports. These may not reflect the extent of integration of qualitative and quantitative findings.

Conclusions

Well conducted qualitative studies can support trial design and improve our understanding of the effects of complex interventions and the mechanisms through which changes occur. However, qualitative studies remain relatively uncommon alongside trials of complex interventions. Most of the qualitative studies were carried out before the trial, had important methodological shortcomings, and the findings were poorly integrated with those of the trials. This study highlights ways in which the quality and usefulness of qualitative studies carried out alongside randomised controlled trials can be improved (see bmj.com).

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Competing interests: ADO was an investigator for two of the included trials and CG worked in the unit in which these trials were coordinated.

Ethical approval: Not required.

1 Hawe P, Shiell A, Riley T, Gold L. Methods for exploring implementation variation and local context within a cluster randomised community intervention trial. *J Epidemiol Community Health* 2004;58:788-93.
2 Oakley A, Strange V, Bonell C, Allen E, Stephenson J, Team RS. Process evaluation in randomised controlled trials of complex interventions. *BMJ* 2006;332:413-6.
3 Campbell M, Fitzpatrick R, Haines A, Kinmonth A-L, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000;321:694-6.
4 Bero L, Eccles M, Grilli R, Grimshaw J, Gruen R, Mayhew A, et al. Cochrane Effective Practice and Organisation of Care Group. About the Cochrane Collaboration (Cochrane Review Groups (CRGs)). *Cochrane Library* 2007;(1).
5 Cochrane Effective Practice and Organisation of Care Review Group. *The data collection checklist*. Ottawa: Cochrane Effective Practice and Organisation of Care Review Group, 2007.
6 Critical Appraisal Skills Programme (CASP). Making sense of evidence: 10 questions to help you make sense of qualitative research. 2007. www.phru.nhs.uk/learning/casp_qualitative_tool.pdf.
7 Rousseau N, McColl E, Eccles M, Hall L. Qualitative methods in implementation research. In: Thorsen T, Makela M, eds. *Changing professional practice. Theory and practice of clinical guidelines implementation*. Copenhagen: Danish Institute for Health Services Research and Development, 1999.
8 Oakley A, Strange V, Stephenson J, Forrest S, Monteiro H. Evaluating processes. A case study of a randomized controlled trial of sex education. *Evaluation* 2004;10:440-62.
9 Riley T, Hawe P, Shiell A. Contested ground: how should qualitative evidence inform the conduct of a community intervention trial? *J Health Serv Res Policy* 2005;10:103-10.
10 Glasgow RE, Lichtenstein E, Marcus AC. Why don't we see more translation of health promotion research to practice? Rethinking the efficacy-to-effectiveness transition. *Am J Public Health* 2003;93:1261-7.
11 Eccles M, Grimshaw J, Walker A, Johnston M, Pitts N. Changing the behavior of healthcare professionals: the use of theory in promoting the uptake of research findings. *J Clin Epidemiol* 2005;58:107-12.
12 Farmer A, Grimshaw J, Mayhew A, McGowan J, Graham I, Driedger M, et al. *Systematic reviews of knowledge translation interventions: contributions of process evaluations and contact with authors. CCOHTA final performance report*. Ottawa: University of Ottawa, 2005.
13 Oxman AD, Fretheim A, Flottorp S. The OFF theory of research utilization. *J Clin Epidemiol* 2005;58:113-6; discussion 117-20.
14 Perkins M, Jensen P, Jaccard J, Gollwitzer P, Oettingen G, Pappadopulos E, et al. Applying theory-driven approaches to understanding and modifying clinicians' behavior: what do we know? *Psychiatr Serv* 2007;58:342-8.
15 West R. Time for a change: putting the transtheoretical (stages of change) model to rest. *Addiction* 2005;100:1036-9.

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Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study

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STUDY QUESTION Is there any association between selective serotonin reuptake inhibitors (SSRIs) taken during pregnancy and congenital major malformations?

SUMMARY ANSWER There is an increased prevalence of septal heart defects among children whose mothers were prescribed an SSRI in early pregnancy, particularly sertraline, citalopram, or more than one type of SSRI.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The teratogenic effects of specific SSRIs are unconfirmed. The study found prescriptions for sertraline, citalopram, or more than one type of SSRI were associated with an increased prevalence of septal heart defects.

Participants and setting

493 113 children born in Denmark, 1996-2003.

Design, size, and duration

This was a population based cohort study. We categorised major malformations according to Eurocat (European Surveillance of Congenital Anomalies) with additional diagnostic grouping of heart defects. Nationwide registers on medical redemptions (filled prescriptions), delivery, and hospital diagnosis provided information on mothers and newborns. We included all children born in 1996-2003, and follow-up data were available to December 2005.

Main results and the role of chance

Redemptions for SSRIs were not associated with major malformations overall but were associated with septal heart defects (odds ratio 1.99, 95% confidence interval 1.13 to 3.53). For individual SSRIs, the odds ratio for septal heart defects was 3.25 (1.21 to 8.75) for sertraline, 2.52 (1.04 to 6.10) for citalopram, and 1.34 (0.33 to 5.41) for fluoxetine. Redemptions for more than one type of SSRI were associated with septal heart defects (4.70, 1.74 to 12.7). The absolute increase in the prevalence of malformations was low—for example, the prevalence of septal heart defects was 0.5% (2315/493 113) among unexposed children, 0.9% (12/1370) among children whose mothers were prescribed any SSRI, and 2.1% (4/193) among children whose mothers were prescribed more than one type of SSRI.

Bias, confounding, and other reasons for caution

Induced or spontaneous abortions might have introduced selection bias if the drug reduces the survival of a fetus or if exposed women undergo more intensive screening. Late abortion (after 12 weeks of pregnancy) because of septal heart defects, however, would not be granted in Denmark. The estimates could be biased if children of women with depression or with a specific pharmacological treatment for a depression were likely to be examined more thoroughly than other children. The study adjusted for potential confounding factors, but residual confounding or unmeasured confounding might still be present. We had no information on the severity of the depression, and potential confounding by indication is impossible to rule out in a non-randomised design. The results depend on a correlation between redemptions of prescriptions and drug use. Non-compliance, if some of the "exposed" were in fact unexposed, and use of antidepressant medication without prescription would result in underestimation of a true association.

Generalisability to other populations

The study used nationwide registries with almost complete follow-up of liveborn infants, and we expect a high degree of generalisability to comparable populations.

Study funding/potential competing interests

This work was funded by a grant from the Lundbeck Foundation, an independent foundation supported by the pharmaceutical company, Lundbeck. The Lundbeck Foundation had no role in the design and conduct of the study; the collection, analysis, interpretation of the data; or the preparation, review, or approval of the manuscript.
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LIKELIHOOD OF MALFORMATIONS ACCORDING TO TWO OR MORE PRESCRIPTIONS FOR SSRI

Birth defects	No of unexposed infants (n=493 113)	Fluoxetine (n=348)		Citalopram (n=460)		Paroxetine (n=299)		Sertraline (n=259)		More than one type of SSRI (n=193)	
		No of infants	OR (95% CI)	No of infants	OR (95% CI)	No of infants	OR (95% CI)	No of infants	OR (95% CI)	No of infants	OR (95% CI)
Cardiac malformations	3988	2	0.77 (0.19 to 3.11)	6	1.75 (0.78 to 3.93)	3	0.88 (0.22 to 3.55)	5	2.36 (0.97 to 5.72)	5	3.42 (1.40 to 8.34)
Septal heart defects	2315	2	1.34 (0.33 to 5.41)	5	2.52 (1.04 to 6.10)	1	0.76 (0.11 to 5.43	4	3.25 (1.21 to 8.75)	4	4.70 (1.74 to 12.7)

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Thigh circumference and risk of heart disease and premature death: prospective cohort study

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STUDY QUESTION Is thigh size independently related to cardiovascular and coronary heart disease or premature death and is there a threshold for effect?

SUMMARY ANSWER Smaller thigh size is associated with an increased risk of cardiovascular morbidity and early mortality independently of abdominal and general obesity and lifestyle and cardiovascular risk factors. There was a threshold effect, with a greatly increased risk of premature death associated with thigh size below around 60 cm.

Participants and setting
A random subset of 1436 men and 1380 women aged 35-65 participating in the Danish MONICA project.

Design, size, and duration
Prospective observational cohort study with Cox proportional hazards model and restricted cubic splines. Participants were examined in 1987-8 for height, weight, and thigh, hip, and waist circumference, and body composition by impedance. Those initially free from coronary heart disease, stroke, and cancer were followed up through personal identification numbers for an average of 10 years for incidence of cardiovascular and coronary heart disease, and for 12.5 years for total mortality.

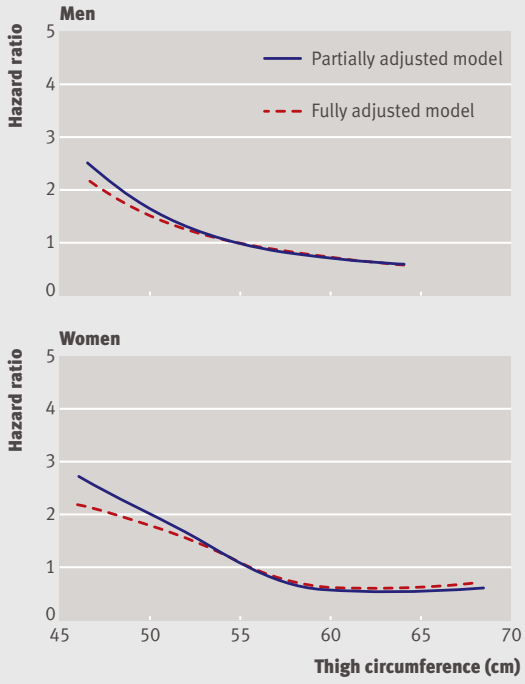
Main results and the role of chance
During the 12.5 years of follow-up 257/1436 men (crude rate 3.3/1000) and 155/1380 women (8.0/1000) died. Smaller thigh circumference was independently related to total death and cardiovascular and coronary heart diseases for men and to total death for women. In both men and women, the risk was more highly related to thigh circumference than to waist circumference or body mass index (BMI). Furthermore, there was a threshold effect in the curves for all end points, suggesting the existence of a critically low thigh circumference. This threshold was 62 cm for both men and women in relation to total mortality, 56 cm in relation to cardiovascular and coronary heart diseases for men, 68 cm in relation to cardiovascular disease for women, and 60 cm in relation to coronary heart disease for women. Above these thresholds, the protective effect of having larger thighs on survival and morbidity from cardiovascular and coronary heart diseases was no longer related to the size of the thighs, whereas below the threshold the risk was greatly increased. All findings were seen both after adjustment for smoking, physical activity, education, menopause (for women), BMI, and waist circumference (partially adjusted model) or further adjustment for alcohol intake, systolic blood pressure, and total cholesterol and triglyceride concentrations (fully adjusted model).

Bias, confounding, and other reasons for caution
The fact that associations were independent of percentage body fat as well as abdominal obesity suggests that the risk with smaller thighs might be associated with too little muscle mass in the region. Because we did not measure tissue composition of the thighs we could not study this question.

Generalisability to other populations
Our results show that there might be an increased risk of premature death related to thigh size. Furthermore, there seems to be a threshold effect of a thigh circumference around 60 cm, but this needs confirmation in other population groups before the results can be generalised. The measure of thigh circumference might be a relevant anthropometric measure to help general practitioners in early identification of individuals at an increased risk of premature morbidity and mortality.

Study funding/potential competing interests
The study was funded by the Danish Medical Research Council. Both researchers were independent of the funding agency.

HAZARD RATIO FOR TOTAL DEATH ACCORDING TO THIGH CIRCUMFERENCE



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