

## SYSTEMATIC REVIEWS

# The effect of conservative treatment of urinary incontinence among older and frail older people: a systematic review

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## Abstract

**Background:** urinary incontinence (UI) is a common symptom among older people, with a higher prevalence among frail older persons living in nursing homes. Despite consequences such as reduced health and quality of life, many older people do not seek help for their symptoms, resulting in missed opportunity for treatment.

**Objective:** the aim of this study was to investigate the evidence and the effect of conservative treatment of UI and the quality of life among older and frail older persons.

**Methods:** a systematic review of randomised controlled studies and prospective, non-randomised studies was conducted, evaluating interventions of conservative treatment of UI in an older population (65 years or older). A total of 23 studies fulfilled the inclusion criteria and 9 were of high or moderate quality. Fourteen studies were of low quality and were therefore excluded from the analysis.

**Results:** documented and effective conservative treatments are available even for older persons with UI. Pelvic muscle exercise, physical training in combination with ADL, prompted voiding and attention training, and help to toilet are important treatments. In some studies, however, the evidence of effectiveness is limited.

**Conclusions:** this systematic review concludes that there are conservative treatments for UI for older and frail older persons that reduce leakage and increase quality of life. There is however a need for further high-quality studies.

**Keywords:** urinary incontinence, older and frail older, conservative treatment, systematic review, bladder training, pelvic floor exercise, prompted voiding, toilet assistance, older people

## Introduction

Urinary incontinence (UI), defined by the International Incontinence Society (ICS) as ‘any urinary leakage’ [1], is a common symptom among older people. The prevalence is estimated to be 30–40% among persons >65 years of age

living in their own accommodation [2, 3] with a higher prevalence among frail older persons living in nursing homes [4]. The problem affects quality of life and causes dependency [5, 6], sleep disturbance [6] and influences the person’s dignity and mood [4]. Treatments that have shown effects are pelvic muscle exercise [7], pharmacological treatment for an

overactive bladder [8] as well as surgery for stress UI [9]. Unfortunately, these studies were performed among younger individuals. However, randomised controlled trials and intervention studies are rare among older and frail older persons [10]. For this group, other treatment options such as conservative treatments can be considered.

Frail older persons can be defined according to Wagg *et al.* [10] as ‘those  $\geq 65$  years of age with a clinical presentation or phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition and endurance’. UI among older persons is often a complex problem associated with co-existing illnesses and co-morbidity [11]. Therefore, they may be dependent on assistance from healthcare staff in their personal daily living arrangements, including incontinence aids and toileting.

Even though the condition of UI is common among older persons and especially frail persons, the lack of evidence on how to treat and effectively care for them is striking. There are three Cochrane reviews (with a total of 9 trials) on conservative treatment of UI using prompted voiding (4 trials), timed voiding (2 trials) and habit training (3 trials). Prompted voiding and timed voiding showed reduced leakage (timed voiding, statistical significant only for night time). No improvement was seen after habit training. However, these reviews do not explicitly define treatment among older and frail older persons [12–14].

Four systematic reviews have evaluated conservative treatment focused on older and frail older persons [15–18]. Fink *et al.* [15] and Flanagan *et al.* [16] focused on interventions among nursing home residents while Roe *et al.* [17] and Talley *et al.* [18] focused on community-dwelling elderly. Among frail older persons in nursing homes, prompted voiding, alone or combined with physical or behavioural therapies, proved to have short-term improvements on UI [15, 16]. Among community-dwelling older persons, the evidence was limited, but incontinence pads and toileting programmes were most commonly used [17, 18]. In 2010, the Swedish government performed the ‘Swedish Council on Health Technology Assessment’ (SBU), an assignment that undertook a systematic review of reliable studies investigating treatments of the older and frail older persons with UI. The aim of this systematic review was therefore to investigate the effect of conservative treatment of UI focused on leakage episodes and quality of life among older and frail older persons.

## Materials and methods

### Design

A systematic review of randomised controlled studies (RCTs) and prospective, non-randomised studies (NRS) was conducted to evaluate interventions of conservative treatment of UI in older and frail older persons.

### Search strategy and selection criteria

To capture literature of older and frail older persons, various synonyms of ageing and living circumstances were used,

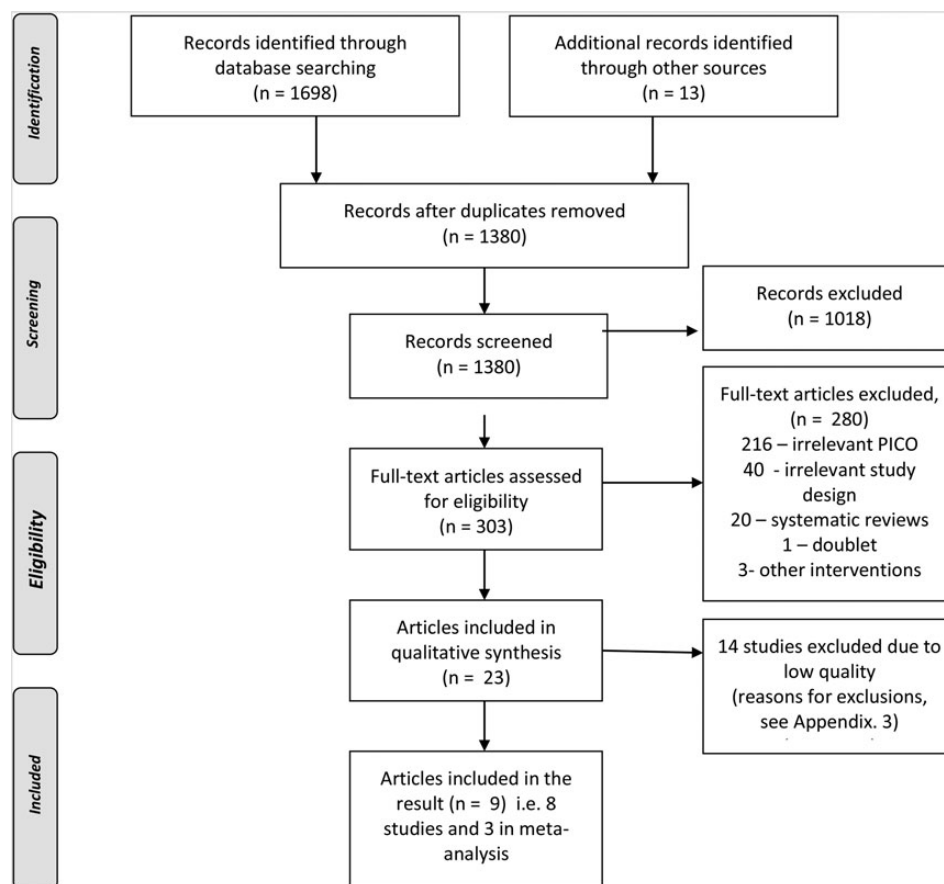
such as ‘aged, aged 80 and over, frail elderly, vulnerable elderly, seniors, community-dwelling, nursing home, care home etc’ (Supplementary data, Appendix S1, available in *Age and Ageing* online). Studies were identified through key word searches in PubMed (NLM), EMBASE (Elsevier), Cochrane Library (Wiley), Cinahl (EBSCO) from 1st January 1966 up to 1st November 2013. Since SBU published a HTA report (health technology assessment) in 2000 examining treatment for UI, studies published in 1997 or prior to this date were specifically identified in that report [19]. The database search was complemented by a search of reference lists, books and websites. The search string is described in Supplementary data, Appendix S1, available in *Age and Ageing* online. Two reviewers (K.S. and U.M.), with clinical and research expertise, independently screened titles and abstracts using standard eligibility criteria.

If either or both of the reviewers considered a study potentially eligible, full-text copies were retrieved. The two reviewers independently screened studies for inclusion based on the eligibility criteria. Consensus was achieved for eligibility. The risk of bias for each study was assessed using a structured professional judgement procedure that is in accordance to the standard practice stipulated by the Swedish Council on Health Technology Assessment (SBU). Studies were scored as low, moderate or high risk of bias (Supplementary data, Appendix S2, available in *Age and Ageing* online). Only studies achieving moderate to low risk of bias were included in for further analyses and meta-analysis. The reasons for high risk of bias were for example: high dropout rates, differences between groups at baseline, unclear selection of participants. References of the 14 excluded articles with reasons for exclusions are added to Supplementary data, Appendix S3, available in *Age and Ageing* online. No contact was made with authors to obtain unpublished data.

For data synthesis, Rev Man (5.1) was used, by using an Inverse Variance and random effects model, due to clinical heterogeneity. For dichotomous outcomes, the risk difference (RD) and the 95% CI were estimated. For continuous outcomes, the mean difference (MD) and the 95% CI were estimated. The conclusions were based on a synthesis of the research evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [20, 21] (Supplementary data, Appendix S1–S3, available in *Age and Ageing* online).

### Study eligibility

All RCT of conservative treatment and prospective, non-randomised studies (NRS) for UI in older and frail older population were included in this systematic review. The study population were required to be 65 years of age or older with UI. The control groups had to undergo ordinary care or other treatment. Eligible outcomes were episodes of incontinence/urine leakage, adverse events and quality of life (QoL). Each group, intervention and control, had to include at least 20 subjects. Conservative treatment included complex interventions, toilet training, behaviour therapy, prompted voiding,



**Figure 1.** Flow chart of literature review of effect of conservative treatment on urinary incontinence and quality of life. PICO = P (population), I (intervention), C (control group), O (outcome).

environmental, complementary therapies, pelvic floor exercise (PFE), bladder training and electrical stimulation. Only studies written in English were included. The flow diagram of the literature search is shown in Figure 1. One study was published in two papers, and therefore, the summary of results presented in Table 1 shows data from eight studies.

## Results

In total 23 studies fulfilled the eligibility criteria, but 14 of these were classified as low quality (high risk of bias) and were therefore not included in the analysis. The main reasons were a high dropout rate, a significant difference between intervention and control groups, a lack of description of randomisation procedure and blinding or small populations. In the remaining nine studies out of a total of 895 persons, the following interventions were found: complex interventions such as attention training and toilet assistance in combination with functional training [22, 23] or structured patient education [24, 25]. Other interventions were physical training in combination with ADL training [26, 27] and PFE in combination with physical training [28–30]. The interventions, populations, outcome measures and biases are presented in Table 1. None of the included studies reported any adverse events. Interventions with alternative medicine (such as acupuncture,

herbal medicine, homeopathy, yoga, mind–body therapy, etc.), electric stimulation and environmental (such as different staff management, occupational therapy, environmental alteration or barriers, etc.) were also included in the literature search, but none fulfilled the inclusion criteria.

## Older persons living at home

### Structured patient education

One study that fulfilled the inclusion criteria had investigated patient education (presented in two publications). The persons included were living at home, had a mean age of 74.4 years and 7–18% were dependent on help in personal activities of daily living (PADL) or instrumental activities of daily living (IADL) [24, 25].

The frequency of micturition decreased during the day, but not at night in the intervention group. They also noted a positive effect in finding toilets, the frequency of changing clothes and the use of protective aids. However, there were no significant effects on urinary leakage episodes (MD = −2.35, CI −5.30, 0.60). There were no differences in general quality of life, but there proved to be an increase in symptom-specific quality of life in the intervention group, i.e. social life, RD−0.13 (−0.25, −0.01) and bother of unpredictability, RD−0.42 (−0.22, −0.09).

**Table 1.** Overview of populations, interventions in study and control group in the included studies as well as the outcome measures and study quality

Author, Country	Population	Intervention	Control	Outcome results	Study quality Design Compliance
Kim <i>et al.</i> [28], Japan	Urban community living women with SUI living age $\geq 70$ , $n = 70$ (drop out I = 4, C = 3) Mean age: I = 76.6, C = 76.6 years <i>Severity of urinary incontinence</i> Urinary leakage $\geq 1$ per month and leakage associated with physical exertion	Exercise class aimed at enhancing PFM and fitness. Duration of the exercise was 1 h/session, twice a week. The intervention group was followed for 1 year. <i>Duration:</i> 3 months	To live a normal life and to refrain from special exercises aiming to increase muscle strength (not only PFM) or walking speed, to decrease BMI or to improve their dietary habits. <i>Duration:</i> 3 months	<i>Subjective incontinence</i> % cure (based on interviews, cured = IE disappeared) Urinary leakage score (points)	Moderate RCT Compliance: 69.7%
Kim <i>et al.</i> [29], Japan	Community-dwelling women, age $\geq 70$ with SUI, UI or MUI $n = 127$ (dropout: I = 4, C = 3) Mean age I = 76.1, C = 75.7 years <i>Severity of urinary incontinence</i> Urine leakage $\geq 1$ per week	Multi-dimensional exercise treatment twice a week. Stretching, pelvic floor exercise, fitness exercise <i>Duration:</i> 3 months with follow-up after 7 months	General education class once a month <i>Duration:</i> 3 months with follow-up after 7 months	<i>Subjective Incontinence</i> % cure (complete cessation of urine leakage episodes), Urine leakage score (5-point scale based on self-reported urinary diaries)	High RCT Compliance: 70.3%
McFall <i>et al.</i> [24, 25], USA	Community-dwelling women aged $\geq 65$ with UI $\geq 3$ months $n = 145$ (drop out I = 23, C = 15) Mean age: I = 73.9, C = 75.6 years <i>Severity of urinary incontinence</i> No information	The program's guiding strategies included (i) behavioural therapies of proven efficacy, (ii) established theories and methods of behavioural change, (iii) a train-the-trainer model for staff of existing health agencies, and (iv) delivery of the program to small groups rather than individuals. <i>Duration:</i> 9 weeks	Usual care <i>Duration:</i> 9 weeks	<i>Objective incontinence</i> UIE/week (mean) Frequency of micturition/week, diurnal (mean) and nocturnal (mean) % change in UIE <i>Quality of Life, 9 weeks</i> Impact of UI on individual Items (%)	Moderate RCT Compliance: No information
Schnelle <i>et al.</i> [22], USA	Incontinent nursing home residents, able to follow a one-step instruction $n = 190$ (drop out I = 18, C = 22) Mean age I = 87, C = 88 years 83.5% women <i>Severity of urinary incontinence</i> (% wet pads) I: 37%, C: 34% (SD 21–23)	Incontinence care integrated with exercise every 2 h between 8 and 16 5 days a week (FIT-intervention) Before or after incontinence care, staff encouraged to walk/wheel their chairs and to repeat sit-to-stands up to eight times. Once/day—upper body resistance training (arm curls or arm raises). Fluid offer and after each care episode. <i>Duration:</i> 32 weeks	No info (usual care) <i>Duration:</i> 32 weeks	<i>Objective Incontinence</i> UI frequency (% checked wet pad) Appropriate urine toileting ratio (%)	High RCT Compliance: No information
Schnelle <i>et al.</i> [23], USA	Incontinent nursing home residents $n = 125$ (drop out I = 7, C = 6) Mean age I = 85.8, C = 86.1 years 82.5% women <i>Severity of urinary incontinence</i> Proportion of wet checks (mean (SD)) I = 0.33 (SD 0.19), C = 0.33 (SD 0.20)	Toileting assistance: checked for incontinence and prompted to use the toilet, prompted to exercise- repeat sit-to- stands and walking or wheelchair propulsion for up to 5 min per care episode and choice of food and fluid snacks every 2 h, 8 h a day, 5 days per week <i>Duration:</i> 3 months	No info (usual care) <i>Duration:</i> 3 months	<i>Objective Incontinence</i> Frequency of UI (% of checks based on 10-day assessment) Appropriate toileting (no. of voids in toilet divided by total no. of voids)	Moderate RCT Compliance: No information

Continued

Table I. Continued

Author, Country	Population	Intervention	Control	Outcome results	Study quality Design Compliance
Sherburn <i>et al.</i> [30], Australia	Community-dwelling women, age ≥65, with urodynamic verified SUI <i>n</i> = 83 (drop out I = 2, C = 5) Mean age: I = 71.6, C = 72 years <i>Severity of urinary incontinence</i> UI perceived as a problem	Individual assessment with physiotherapist (0–4 times), and a home program. Group educational session's once a week. The 1 h weekly session: intensive PFMT, combining motor control, strength, endurance, power and functional training. Daily PFMT program at home. Duration: 5 months	Weekly group session with an education and gentle exercise component. Duration: 5 months	<i>Subjective Incontinence</i> ICIQ-SF total scores, VAS score <i>Objective Incontinence</i> Stress test-cough (g) Stress test-brace/cough (g) Cure (%) 7 days accident diary <i>Quality of life</i> AQoL total score <i>Objective Incontinence</i> Pad test (% difference) Mean % difference	High RCT Compliance: 93.1% (C) 96.8% (I)
Van Houten <i>et al.</i> [26], The Netherlands	Women living in nursing home, age ≥65 <i>n</i> = 57 (drop out I = 4, C = 6) Mean age: I = 80.9, C = 84.5 years <i>Severity of urinary incontinence</i> UI episodes ≥2/week and for I ≥ 3 months PAD test I: 462 ml, C: 448 ml	Training program for mobility and toileting skills on individual basis 3 times per week for 30 min. The training program ended if a participant was able to perform all targeted tasks within the threshold time. Duration: 8 weeks	No info (usual care) Duration: 8 weeks	<i>Objective Incontinence</i> Pad test (% difference) Mean % difference	Moderate RCT Compliance: 80%
Vinsnes <i>et al.</i> [27], Norway	Nursing home residents, age ≥65 Staying in NH for >3 months <i>n</i> = 98 (dropout I = 13, C = 17) Mean age I and C = 84.3 years <i>Severity of urinary incontinence</i> 24 h PAD test I: 576 ml, C: 424 ml	Training programme in physical activity and ADL training. Training in transfer and walking ability, balance, muscle strength and endurance was offered individual and groups, while ADL training was performed when residents needed help during meals, with personal care or dressing. Duration: 3 months	Usual care Duration: 3 months	<i>Objective Incontinence</i> 24 h Pad test	Moderate RCT Compliance No information



**Table 2.** Effects and grade of evidence of different interventions in older persons living at home and frail older persons on urinary incontinence and quality of life

Intervention among elderly living at home	Pelvic floor exercise in combination with physical training compared with education or bladder training			Structured education
Study	Kim <i>et al.</i> [28]	Kim <i>et al.</i> [29]	Sherburn <i>et al.</i> [30]	Mc Fall <i>et al.</i> [24, 25]
Assessment	Cure rate (%) Urinary leakage score	Cure rate (%) Urinary leakage score	Cure rate (%) ICIQ-SF score VAS score	Urinary leakage episodes/week
Effect UI frequency	I: 54.5% C = 9.4% RD = 0.45* MD = -0.90*	I = 39.3% C = 1.6% RD = 0.42* MD = -1.20*	RD = 0.23* MD = -2.60* MD = -1.50*	I = 3.55, C = 5.9 MD = -2.35 (CI -5.30 to 0.60)
Follow-up time	3 months	7 months	5 months	9 weeks
Overall assessment/ Quality of evidence		Urinary leakage Reduced urinary leakage ⊕⊕⊕○		Urinary leakage No significant difference ⊕○○○
Overall assessment/ Quality of evidence		Quality of life Improved symptom-related quality of life after 5 months ⊕⊕⊕○ No difference in general quality of life ⊕⊕○○		Quality of life No significant difference in health-related QoL. Significant difference in symptom-specific quality of life ⊕○○○
Interventions among frail elderly	Attention training and help to toilet in combination with functional exercise		Physical training in combination of ADL training	
Study	Schnelle <i>et al.</i> [22]	Schnelle <i>et al.</i> [23]	Van Houten <i>et al.</i> [26]	Vinsnes <i>et al.</i> [27]
Assessment	Controlled wet pads (%)	Treatment coefficient	Leakage test: % difference (mean—is less urinary loss)	Leakage test
Effect UI frequency	I = 23%, C = 35% P = 0.0005 Z = 3.46, MD = -12.00 (CI -18.79 to -5.21)*	UI = -0.07, P < 0.05 t = -1.95	24 h: -8% P = 0.07 (CI -1.046 to 0.047) Day time: -22%, P = 0.47 Night time: -35%, P = 0.15	I: 489 ± 375 ml; C: 624 ± 454 ml, P = 0.18 MD = -135.00 (CI -333.56 to -63.56)**
Follow-up time	32 weeks	3 months	8 weeks	3 months
Overall assessment/ quality of evidence	Reduced urinary leakage episodes ⊕⊕○○		No significant differences in urinary leakage ⊕○○○	

⊕⊕⊕○, moderate quality of evidence; ⊕⊕○○, low quality of evidence; ⊕○○○, very low quality of evidence, \* = significant difference  $P < 0.05$ , \*\* = significant difference after adjusting for baseline differences.

In conclusion, positive effects due to patient education were found, but there are insufficient studies showing that patient education has a significant effect on the amount of urinary leakage or quality of life (Table 2).

### PFE in combination with physical exercise

Three studies used the intervention of PFE in combination with physical exercise in groups of women living at home (mean age 77, 76 and 82 years) [28–30].

The results showed a significantly higher cure rate and a subjectively lower urinary leakage score in the intervention group (Table 2). Additionally the participants lost weight (reduced BMI, body mass index and waistline) and showed an improvement in walking speed [28, 29].

In the study by Sherburn *et al.* [30], the results showed that the intervention group had statistically better results, although both groups showed improvements. The intervention groups had a significantly higher cure rate and subjectively less bother (Table 2).

The weighted effect of all three studies showed that intensive PFEs in combination with physical exercise have an effect

on the amount of incontinence episodes in all types of UI in older persons living at home. The effect is valued as moderately strong and statistically significant ( $P < 0.0001$ ) (Figure 2).

PFE in combination with other physical exercise reduced the number of incontinence episodes in all types of UI among older persons in comparison to bladder training and education. The quality of evidence is moderate.

PFE in combination with other physical exercise improved symptom-related quality of life compared with bladder training and education. The quality of evidence is moderate. No difference could be seen in the general quality of life. Conclusive scientific evidence is limited (Table 2).

### Frail older persons

#### Attention training and help to toilet, in combination with functional exercise

Two studies [22, 23] examined frail older persons (mean age 85 and 88 years) with urinary or combined incontinence (urine and faecal) living in nursing homes. The interventions required extra personnel due to the fact that each intervention was estimated to take ~20 min.

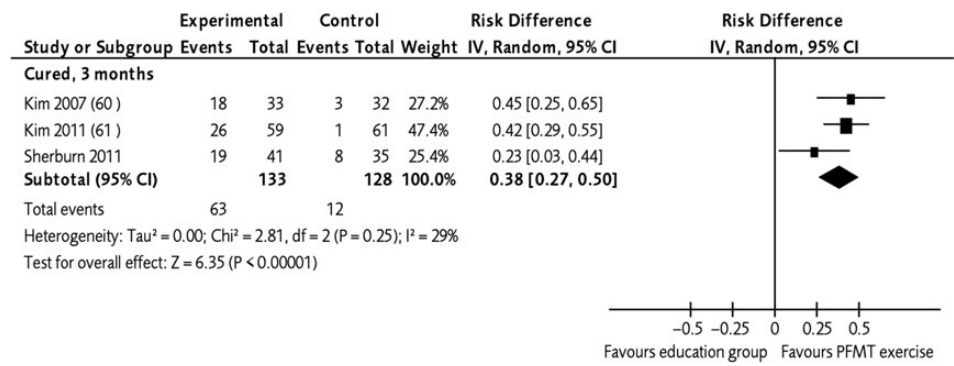


Figure 2. Effect of intensive pelvic floor training.

The intervention group had significant objective improvement in the frequency of incontinence episodes and more frequent successful toilet visits for urine. The intervention also had positive effects on successful toilet visits for bowel emptying. They improved their walking ability, could more easily stand by themselves without assistance and had improved their arm strength. Those who were not able to walk had increased their ability to operate their wheelchair. The patient intake of fluid increased in both studies [22, 23] and the calorie intake increased in the second study [23] (Table 2).

The weighted analysis of the two studies showed that attention training, i.e. being reminded to make toilet visits and being helped to go to toilet every hour, in combination with functional exercise, had effect on urinary leakage in frail older persons. The effect was moderate but statistically significant. However, it is unclear whether the same intervention had any effect on quality of life (Table 2).

Physical exercise in combination with training in ADL functions

Two studies investigated frail older persons with mean ages of 82.7 [26] and 85.7 years [27] living in institutions or with supportive day care. The results showed that time to toilet reduced significantly during the daytime ( $P = 0.05$ ), but no significant difference was seen in the results of the 24-h pad test or in the objective leakage score. However, leakage episodes increased in the control group compared with the intervention group. After controlling for baseline differences such as age, sex and function status, the difference in urinary leakage was statistically significant (Table 2).

The weighted analysis from the two studies showed no significant reduction of the frequency of urinary leakage episodes or quality of life, with physical training in combination with ADL training (Table 2).

The study conducted by Houten *et al.* [26] did not specify whether extra personnel were required to complete the study. In the study undertaken by Vinsnes *et al.* [27], an additional occupational therapist worked together with ordinary staff.

Discussion

Conservative treatment is effective for older and frail older people with UI. Interventions of pelvic muscle exercise, physical

training in combination with ADL, prompted voiding, attention training and help to toilet are important treatments, but the quality of evidence varied from moderate to low.

Method discussion

A weakness in all of the study cases is an incomplete description of co-morbidity, pharmacological treatment, ADL capacity, etc., which would have been helpful to distinguish older from frail older persons. A mutually accepted definition of how frailty may be defined would be beneficial in helping to construct and evaluate studies among older people. In this systematic review, we have classified those living in institutions as ‘frail older persons’ and those living at home as ‘older persons’. However, as in Sweden and probably in other countries, many frail older persons are cared for in their homes with additional help from the community. The differentiation between living at home and living in an institution is therefore not sufficient to classify frailty. Another definition distinguishes frailty as not being synonymous with co-morbidity or disability [31]. Studies therefore need to have a clear and consistent definition of the study population and of outcomes, as well as unambiguous definitions and descriptions of the intervention and the care in the control group [32].

A problem with conducting RCTs among older and especially frail older persons is the risk of high dropout rates due to severe illness or even death, resulting in studies of high risk of bias and thus low quality. This factor was also demonstrated in this systematic review.

Results discussion

Among older persons living at home, the review showed that PFE in combination with physical training is effective and increases quality of life, both general and symptom specific [28–30]. Also, Brunenberg *et al.* [33] have found that PFE is cost-effective among women >75 years. Therefore, there is a need to increase the knowledge among healthcare providers, as well as among older people and their relatives.

Educational intervention in combination with behavioural intervention had no significant effect on UI or quality of life;

however, further studies are required as there was only one study in this review.

Among frail older people, attention training and help using the toilet in combination with functional exercise had a statistical effect on UI [22, 23]. This data could contribute to practical guidelines in the care of frail older people in nursing homes. The quality of care would be increased and costs incurred by incontinence aids reduced. In a recent review by Vagetti *et al.* [34], it was found that physical activity has a consistent association with quality of life, such as functional capacity, general QoL, autonomy, past, present and future activity and intimacy. The same additional effects may be found when implementing physical exercise in combination with PFE or help to the toilet for older persons with UI.

A limitation in conducting and implementing the results of several studies, as shown in the study examples of Vinsnes *et al.* [27] and Schnelle *et al.* [22, 23], is that extra staff were needed. They conclude that limitations of staff resources are a problem in these studies. On the other hand, it is possible to discuss whether helping patients to the toilet is a staffing problem or a problem of what is a basic human need, irrespective of the staff required. However, if increased staff numbers showed significant improvement on levels of incontinence, these extra resources may be of economic value due to increased integrity and a reduction in the use of incontinence aids.

## Conclusion

This systematic review concludes that there are conservative treatments for UI for the older and the frail older persons that reduce incontinence and increase quality. There is however a need for further high-quality studies. This is essential for guiding clinical practice in the prevention and management of UI among older persons,  $\geq 65$  years of age, and particularly for frail older persons. This demand is especially important because of the rapidly ageing population who face a risk of UI with its associated psychosocial and economic burdens.

## Key points

- PFE together with other physical training is effective and increases quality of life.
- Attention training and toilet assistance reduce leakage episodes among frail older persons.
- Additional functional physical exercise seems to add positive effects on continence as well as quality of life.

## Authors' contribution

All cited authors have made substantial contributions to this article, in discussions before, during and after the reviewing

process, and have critically revised the manuscript, and approved the submitted version.

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## Conflicts of interest

None declared.

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## Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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(The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is given in Supplementary data, available in *Age and Ageing* online.)

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