

Effectiveness of preventive primary care outreach interventions aimed at older people

Meta-analysis of randomized controlled trials

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ABSTRACT

OBJECTIVE To determine the effectiveness of preventive primary care outreach interventions aimed at older people. Knowing whether such interventions are effective could help busy family physicians make choices about which preventive care services to provide.

DATA SOURCES We searched MEDLINE, CINAHL, AgeLine, Cochrane Controlled Trials Register, and EMBASE databases and reviewed the reference lists of retrieved articles.

STUDY SELECTION We included studies of preventive primary care interventions aimed at patients 65 years and older if the studies were randomized controlled trials and if any of the following outcomes was reported: mortality, living in the community, admission to acute care hospitals, and admission to long-term care. We defined preventive primary care outreach as proactive, provider-initiated care, which can be provided by nurses, physicians, other professionals, or volunteers, that is in addition to usual care and is provided in primary care settings. Such care can be provided through home visits, office visits, telephone contacts, or a combination of these methods.

SYNTHESIS We assessed the quality of studies and extracted descriptive information on study populations, interventions, and outcomes for 19 trials involving 14 911 patients. Summary odds ratios were estimated for each outcome using a random effects model.

CONCLUSION This review showed that studies of preventive primary care outreach interventions aimed at older people were associated with a 17% reduction of mortality and a 23% increased likelihood of continuing to live in the community.

EDITOR'S KEY POINTS

- Results of studies evaluating the efficacy of preventive primary care interventions aimed at elderly people living in the community are inconclusive.
- This meta-analysis of 19 randomized controlled trials showed that interventions decreased risk of mortality, and that 36 older people would have to be exposed to such interventions to prevent one death. As a comparison, 63 older people with hypertension would have to be treated for 5 years to prevent one death.
- An increased likelihood of being able to continue to live in the community was also observed among people receiving these interventions.

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As the percentage of older adults in the Canadian population increases,¹ the complexity of care required to support those who choose to remain in the community has increased also.² This situation can create challenges for patients, caregivers, their family physicians, and community agencies.

Several studies conducted over the past decade have evaluated specialty-based models designed to anticipate and detect early health problems in community-dwelling older adults and interventions to improve health outcomes.³ We know that individual preventive actions can be effective for older adults,⁴ but it has been less clear whether proactive models anchored in the primary care sector of the health care system are effective at improving older adults' health outcomes.

Innovative approaches to patient care in the community that address the growing challenge of providing high-quality comprehensive care for older adults require evaluation. This paper reviews the evidence for one such approach, preventive primary care outreach (PPCO). We define PPCO as proactive, provider-initiated care that is in addition to demand-led usual care, is provided in

community primary care settings, and is linked to the usual care system. Its goal is to identify unrecognized problems and people at increased risk and to link those people to appropriate health and social care and support. Family physicians, nurses, or other professionals and volunteers can provide PPCO through home visits, office visits, telephone contacts, or a combination of these methods. Some

Definitions of terms: Pooling of results of primary studies in a meta-analysis can be done using either a fixed-effects model or a random-effects model.

Fixed-effects model: This model restricts inferences to the set of studies included in the meta-analysis and assumes that a single true value underlies all the study results. It takes into account variability within studies, but does not take into account variability between studies.

Random-effects model: This model assumes that the studies included are a random sample of a population of studies addressing the question posed in the meta-analysis. It takes into account variability within studies and variability between studies.

Weighting studies: Results from smaller studies are more subject to the play of chance. By incorporating a weighting scheme, we can reduce the effect of studies with more uncertainty on the final summary estimate of effect.

Heterogeneity: The extent to which results differ from study to study.

Fitted-cell frequencies: The values we would expect in a two-by-two table if all the studies had similar levels of the covariates for which we adjusted.

Source: Guyatt G, Rennie D. *Users' Guides to the Medical Literature. A Manual for Evidence-Based Clinical Practice*. Chicago, Ill: American Medical Association; 2002.

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reports suggest that a preventive approach based on screening those at risk and providing early intervention could help prevent functional decline, promote independence, and control social and health costs.^{5,6} Knowing whether PPCO is an effective approach is important for family physicians as they make choices about which preventive care services to provide in a busy practice.

Results of primary studies of PPCO interventions for older people have been mixed. Only some studies demonstrate benefits that are both clinically important and statistically significant. Previous systematic reviews have examined preventive home visits to older people,^{7,8} home-based support for older people,⁹ comprehensive geriatric assessment,³ and health assessments of older people.¹⁰ These reviews included interventions not consistent with our definition of PPCO (eg, studies used resources not readily available in primary care settings, such as consultation with geriatricians) or studies that did not meet our inclusion criteria (eg, non-randomized trials, or studies of patients after hospital discharge).

This systematic review aimed to determine the effectiveness of PPCO interventions for community-dwelling older people. We were interested in assessing a model of preventive primary care that used only primary care resources and was consistent with current approaches to primary care in the developed world. Our inclusion criteria were carefully developed to ensure commonality of studies in the meta-analysis.

Methods

Data sources. We searched MEDLINE from January 1966 to July 2001, CINAHL from January 1982 to July 2001, AgeLine from January 1978 to July 2001, the Cochrane Controlled Trials Register up to July 2001, and EMBASE from January 1988 to July 2001 for reports of primary research, using the indexing terms “aged” combined with “geriatric assessment” or “preventive medicine” or “home care services” or “risk assessment” and “randomized controlled trial.” Articles were limited to “age 65 and over” and “English language.” Searches were

conducted by two people expert in searching for systematic reviews.

Study selection. Two investigators reviewed the searches and the reference lists of all articles retrieved. The complete texts of all potentially relevant articles were reviewed using the inclusion and exclusion criteria listed in **Table 1**. Teams of two investigators independently abstracted data from all studies that met the eligibility criteria. We attempted to contact authors when data were missing. The methodologic quality of each study was independently assessed by two investigators using the Jadad et al scale, which has demonstrated validity.¹¹ The Jadad et al scale is scored by awarding 1 point for each “yes” response to the following items: randomization is reported; method of randomization is described; double blinding is reported; method used to double blind is described; and withdrawals and drop-outs for each arm are described. A point is subtracted for each “no” response to the following items: randomization method is appropriate; and double-blinding method was appropriate.

Table 1. Inclusion and exclusion criteria

INCLUSION CRITERIA
Most patients were 65 and older
Patients were community dwelling (not living in residential care or nursing homes)
The intervention, preventive primary care outreach, was defined as proactive, provider-initiated care (not in response to a patient health problem or event, such as hospitalization or a fall) that is in addition to usual care
The intervention was provided in an ambulatory primary care community setting
The study design was a randomized trial
At least one of the following patient outcomes was reported: mortality, living in the community, admission to an acute care hospital, and admission to long-term care
EXCLUSION CRITERIA
Patients were selected on the basis of a specific existing condition (eg, dementia or a history of falls)
Patients were part of a posthospital program
The intervention used resources generally available only in secondary care (eg, consultations with geriatricians)

Analysis. Summary odds ratios (ORs) were calculated using methods described by Fleiss.¹² Two-by-two tables were constructed for each outcome in

each study for which data were available. A value of 0.5 was added to each cell of the two-by-two table to adjust for zero cell frequencies.¹³ Summary estimates of effect were calculated by combining individual trial estimates weighted by the inverse of their variances. Both fixed and random effects¹⁴ estimates were calculated. Heterogeneity was assessed using the Q statistic, which follows a chi-square distribution with N-1 degrees of freedom, where N is the number of trials.¹² We defined statistical heterogeneity as $P < .10$.

For each outcome, we analyzed data from the final follow-up assessment period. The denominator used to calculate effect sizes for outcomes was the number of subjects randomized. We also examined the effect of duration of follow up on mortality by calculating summary ORs at 6, 12, 24, 36, and 48 months separately using all possible data. In an exploratory analysis, we examined seven methodologic, patient population, and intervention characteristics that might modify the effect of PPCO (Table 2). To test whether differences in these characteristics influenced the magnitude of treatment effect in studies, we divided the trials into two specified categories for each variable. We used the z score to test for a difference in effect size between the two groups by dividing the difference of the summary log relative risk from both groups by the standard error of the difference.

We used a logistic regression method to adjust for all seven covariates simultaneously.¹⁵ Fitted-cell frequencies were estimated for each study using

logistic regression. These adjusted cell frequencies were then used as input for the standard meta-analysis program to estimate an adjusted summary OR.

Synthesis

The study selection process (Figure 1) yielded 1030 citations. Twenty-two reports of 19 studies met our inclusion criteria.¹⁶⁻³⁶ In 14 studies, samples were selected from primary care practice populations using sampling frames such as practice registries^{17,19-21,23,26-30,32,34-36}; in the other five studies, samples were selected from general population bases using sampling frames such as census lists or health insurance lists.^{22,24,25,31,33} Descriptive details of these 19 studies are shown in Table 3.¹⁶⁻³⁶

Typically, interventions involved an initial health and social assessment or screening of subjects by a professional or volunteer. Subjects in the intervention group received one or more home, telephone, or office contacts by family physicians, nurses, social workers, or volunteers. Interventions included education about health-related matters and referrals to relevant community agencies for health and social services (eg, nursing visits, Meals on Wheels, homemaking), and to family physicians. The frequency of follow-up contacts varied, as did the duration of the intervention (12 to 60 months). Table 3¹⁶⁻³⁶ lists outcomes assessed in the 19 trials included in the meta-analysis.

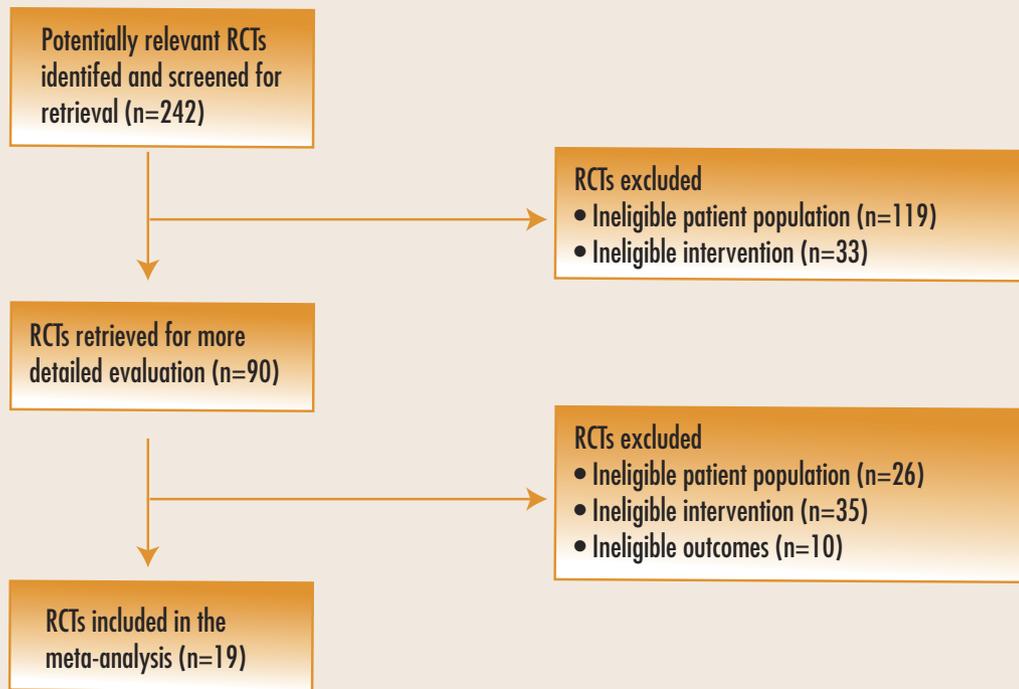
Mortality (19 studies). The summary OR was 0.83 (95% confidence interval [CI] 0.75 to 0.91), a 17% reduction in mortality (Table 4¹⁶⁻³⁶). In all but three studies,¹⁹⁻²¹ the intervention was associated with a reduction in mortality, with exact ORs ranging from 0.25 to 0.91. Heterogeneity of study results was not statistically significant ($P = .39$). Assuming a mortality rate in the absence of intervention equivalent to the overall mortality rate in the control arms of the studies included in our review, PPCO would prevent one death for every 36 elderly people targeted for intervention.

Because the study by Burton et al¹⁶⁻¹⁸ accounted for 28% of the summary estimate, we conducted a sensitivity analysis to determine the effect of this

Table 2. Methodologic, patient population, and intervention characteristics that could modify the effect of a preventive primary care outreach intervention

METHODOLOGIC CHARACTERISTIC
Methodologic quality (score of ≤ 2 vs ≥ 3)
PATIENT POPULATION CHARACTERISTICS
Source of sample (practice-based vs population-based)
Age (mean or median age < 75 years vs ≥ 75 years)
Targeting a high-risk group (targeting vs not targeting)
Geographic area (Canada vs other countries)
INTERVENTION CHARACTERISTICS
Frequency of contacts (once or less per year vs twice or more per year)
Length of follow up (≤ 24 months vs ≥ 36 months)

Figure 1. Study Flow



RCT—randomized controlled trial.

Table 3. Randomized controlled trials that evaluated preventive primary care outreach interventions for older people

STUDY	SAMPLE SIZE AND CHARACTERISTICS	INTERVENTION	INTERVENORS	DURATION OF FOLLOW UP (MO)	OUTCOMES ASSESSED
Burton et al 1995 ¹⁶ and 1997 ¹⁷ ; German et al 1995 ¹⁸ (USA)	4195 people ≥65 y from 102 solo or partnership practices, 12 community group practices, and three medical clinics; 63% women*	Preventive services each year for 2 years that included physical examination, laboratory screening for cancer, immunizations, and counseling for health risks†	Physicians, nurse practitioners, physicians' assistants, osteopaths	48	a,c,d,m,n
Carpenter and Demopoulos 1990 ¹⁹ (UK)	539 people ≥75 y from two general practices: 87% 75-84 y, 13% ≥85 y; 65% women*‡§	Visits over 3 years to complete questionnaire on activities of daily living; if no disability, visits every 6 mo; if some or severe disability, visits every 3 mo†	Volunteers	36	a,c,d,e,g,j,k
Clarke et al 1992 ²⁰ (UK)	523 people ≥75 y living alone from a large group practice of 12 family practitioners*‡§	Visits for 1.25-2 y; minimum of 3 visits in first year. Assistance, tailored to personal requests, included social, financial, housing, nursing and medical services†	Lay community workers	42	a,b,e,l,m
Dalby et al 2000 ²¹ (Canada)	142 people ≥70 y at risk of functional decline on roster of two family physicians; mean age 79 y; 67% women*‡§	Visiting nurse developed care plan with physician, patient, family; follow-up visits and phone calls as needed over 14 months to promote health, provide support, make referrals†	Nurses	14	a,c,m
Hall et al 1992 ²² (Canada)	167 people ≥65 y receiving personal care at home; mean age 78 y; 78% women‡§	Home visits, development of personal health plan, and referral. Frequency of visits varied: average of 4-12 h/y per client†	Nurse	36	a,b,c

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Table 3. Randomized controlled trials that evaluated preventive primary care outreach interventions for older people

STUDY	SAMPLE SIZE AND CHARACTERISTICS	INTERVENTION	INTERVENORS	DURATION OF FOLLOW UP (MO)	OUTCOMES ASSESSED
<i>Continued from previous page</i>					
Hay et al 1998 ²³ (Canada)	619 people ≥65 y listed on a practice roster who screened positive for health concerns or risks; mean age 74; 58% women*§	Referral for follow-up care for issues identified on screening form; such care provided by physician, nurse practitioner, social worker, chiropodist, optometrist, and nurse responsible for giving influenza vaccine	Physicians	24	a,c,e,m,n
Hébert et al 2001 ²⁴ (Canada)	494 people ≥75 y listed on the Quebec health insurance plan identified through mailed questionnaire at risk of functional decline; mean age 80; 64% women‡§	Assessment by nurse who sent results to GP; referral to specialized resources and contact with GP; monthly contact with clients for 1 y†	Nurse	12	a,c,h
Hendriksen et al 1984 ²⁵ (Denmark)	600 people ≥75 y listed on a register of municipal social welfare authorities; median age 78; 62% women‡	Home visits every 3 mo for 3 y; Intervenor visited subjects, conducted assessment, offered referral to and coordination of community services; subjects could telephone to request additional visits†	Medical resident, home nurses	36	a,b,c,d,j,k,m,n
Leveille et al 1998 ²⁶ (USA)	201 people ≥70 y registered in two HMOs and being treated for at least one chronic condition excluding dementia or terminal disease; mean age 77; 56% women*‡§	Targeted multicomponent disability prevention and disease management program at a senior centre for 1 y; nurse met each person to develop health management plan to address risk factors for disability; follow-up visits (average of three) and telephone calls (average of nine); peer support; referral†	Geriatric nurse practitioner, volunteer mentors	12	a,d,f,h,m,n
McEwan et al 1990 ²⁷ (UK)	296 people ≥75 y registered in a general practice*‡	One home visit to complete assessment, give health advice, and make referrals	District nurses	20	a,e,m
Newbury et al 2001 ²⁸ (Australia)	100 people ≥75 y registered in six general practices; median age 79; 63% women*‡	One health assessment in home	Nurse	12	a,c,f,g,h,l
Pathy et al 1992 ²⁹ (UK)	725 people ≥65 y registered with a general practice; mean age 73; 60% women*§	GP mailed questionnaire yearly for 3 y. If responses indicated problems, health visitor made visit to give practical advice, health education, or make referrals	Health visitor	36	a, [†] b, [†] c, d, [†] h,i,l
Schraeder et al 2001 ³⁰ (USA)	941 people ≥65 y with at least one risk factor registered with one of 32 family practice or 19 internal medicine physicians; mean age 76; 73% women*‡§	Home assessment by nurse. Collaborative team generated plan of care. Case assistant provided telephone monitoring, education, health promotion, referral to and coordination of supportive services. Team provided flexible home or office visits over 2 y†	Physicians, nurses, and case assistants	24	a,d,n
Sorensen and Sivertsen 1988 ³¹ (Denmark)	1554 people aged 75, 80, and 85 drawn from the Central National Register; 49% women in intervention group‡	One home visit by social worker and physician. Social worker conducted assessment, referred patients to social services. Physician conducted medical examination	Social worker and physician	60	a, [†] b, [†] c, [†] e,i,l,m
Tulloch and Moore 1979 ³² (UK)	295 people ≥70 from a general practice register; 46% women*‡	Letter sent with medical questionnaire and offer of physical examination (at office or home if required). Patients monitored regularly for 2 y at clinic run by GP, practice nurses, and health visitors	GP, practice nurses, and health visitors	24	a,d,m
van Rossum et al 1993 ³³ (Netherlands)	580 people aged 75-84 y; 58% women‡	Home visits by nurses four times yearly for 3 y with extra visits if necessary; telephone contact; nurses discussed health topics, gave information and advice, and made referrals†	Nurses	36	a, b, [†] c,d,h,l,m,n

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Table 3. Randomized controlled trials that evaluated preventive primary care outreach interventions for older people

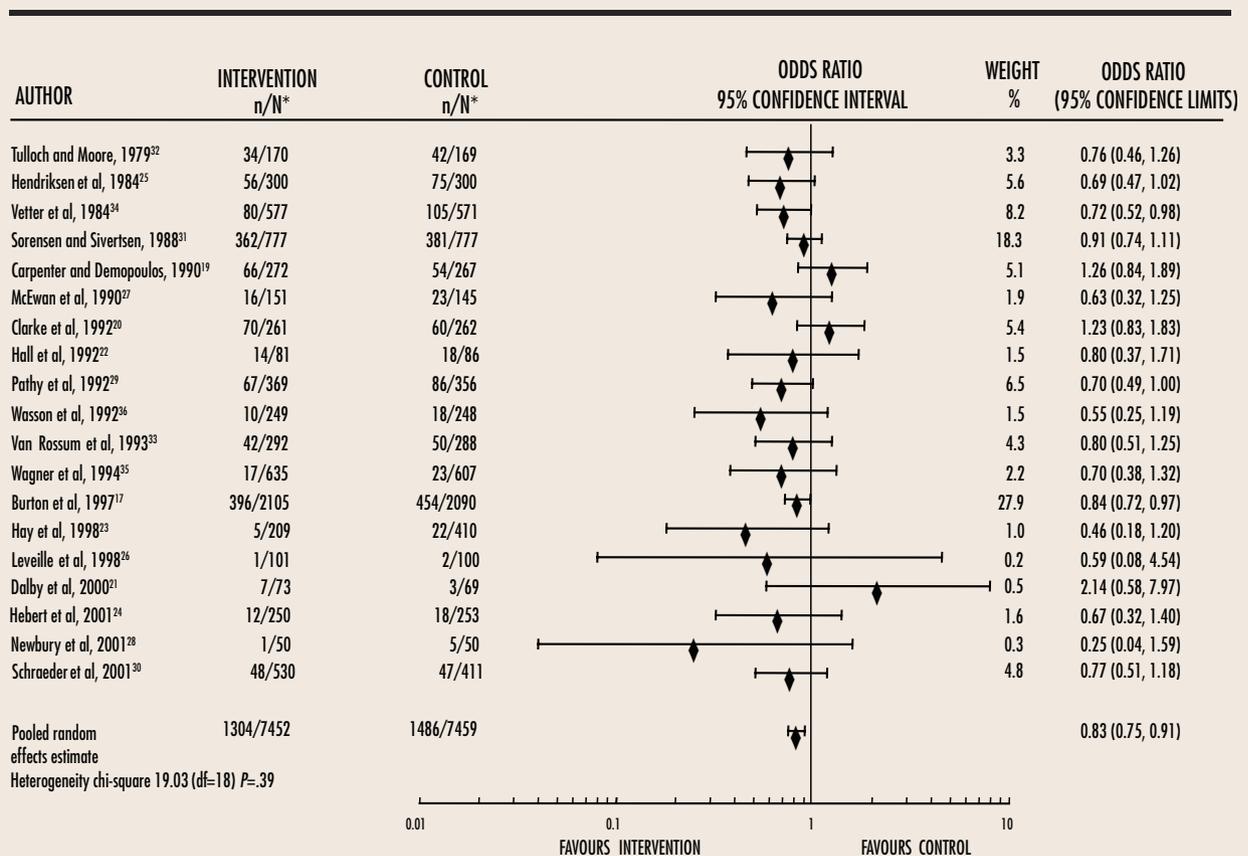
STUDY	SAMPLE SIZE AND CHARACTERISTICS	INTERVENTION	INTERVENORS	DURATION OF FOLLOW UP (MO)	OUTCOMES ASSESSED
<i>Continued from previous page</i>					
Vetter et al 1984 ³⁴ (UK)	1148 people aged 70 y from two general practice registers*	Minimum of one home visit yearly for 2 y to provide health education, preventive counseling, referrals, and follow up	Health visitors	24	a,b ^h c, ¹ f,m
Wagner et al 1994 ³⁵ (USA)	1559 people ≥65 y enrolled in three group health cooperatives; mean age 72.5; 60% women*§	Assessment visit and follow-up interventions targeting risk factors for disability and falls (exercise, alcohol, medication use, hearing or vision). Referrals. One or two follow-up telephone calls; mailed reminders†	Nurses	24	a,g,h
Wasson et al 1992 ³⁶ (USA)	497 men aged ≥54 attending a primary care clinic; mean age 66*	Clinicians doubled their recommended interval for face-to-face follow up and scheduled three intervening telephone contacts†	Internists, physicians' assistants, nurse practitioners	24	a,d,m,n

a—mortality, b—living in the community, c—admission to long-term care, d—admission to acute care, e—activities of daily living, f—depression, g—falls, h—physical function, i—quality of life, j—referral to homemaking, k—referral to Meals on Wheels, l—self-rated health, m—use of health services, n—costs of health services.

*Sample source classified as practice. †Intervention classified as frequent contact. ‡Sample classified as older (age indeterminate in Vetter et al³⁴). §Sample classified as targeted risk group.

¶Additional data obtained from author.

Table 4. Odds ratios for mortality



*n/N = number dying/number studied.

study on the summary OR and the summary OR's precision if this study was removed. The summary OR for mortality without this study was 0.82 (95% CI 0.73 to 0.92), which is very similar to the summary OR and 95% CI with this study included.

Living in the community (seven studies). In all seven trials, patients receiving PPCO interventions were more likely to be living in the community at the end of the study (Table 5^{20,22,25,29,31,33,34}). Summary OR was 1.23 (95% CI 1.06 to 1.43). Heterogeneity of study results was not statistically significant ($P = .22$).

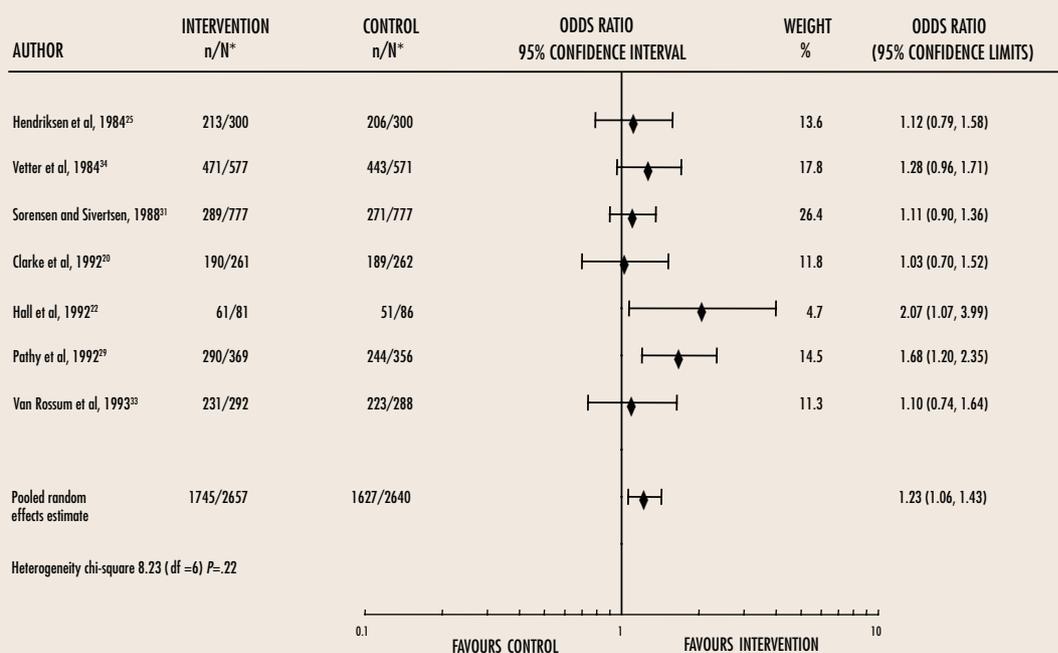
Other outcomes. Summary ORs for admission to long-term care (OR 0.88; 95% CI 0.74 to 1.05) and acute care hospital (OR 1.00; 95% CI 0.85 to 1.16) were not statistically significant (data not shown).

Length of follow up. The summary OR for mortality was significant at 12 months (OR 0.80, 95% CI 0.66 to 0.98) and at 24 months (OR 0.78, 95% CI 0.70 to 0.87) (Table 6).

Exploratory analyses. Study quality and intervention characteristics (frequency of contact, length of follow up) did not modify the effect of PPCO on the outcomes of mortality, living in the community, and admission to long-term care or acute care hospitals. Patient population characteristics (source of sample, age, risk status, and geographic area) did not modify the effect of PPCO on mortality or on admission to long-term care or acute care hospitals. For the outcome of proportion of people living in the community, trials conducted among younger people had significantly higher summary ORs than trials conducted among older people (summary ORs 1.68 and 1.13, respectively, $P = .03$). For the outcome of mortality, the summary OR for trials conducted in Canada was 0.75²¹⁻²⁴ (95% CI 0.46 to 1.22) compared with the summary OR of 0.83 (95% CI 0.75 to 0.92) for trials conducted in other countries ($P = .39$).

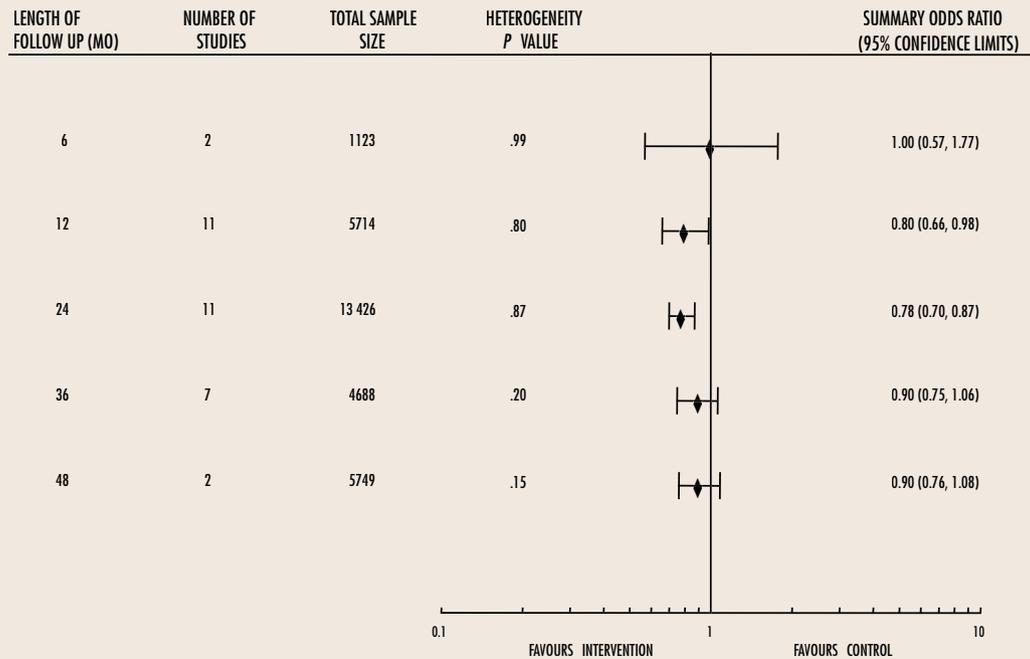
Adjusted analysis. When we adjusted for all covariates listed in Table 2, the adjusted summary random effects ORs for the outcomes of mortality,

Table 5. Odds ratios for living in the community



*n/N = number living in the community/ number studied.

Table 6. Mortality summary odds ratio and 95% confidence intervals by length of follow up



living in the community, and admission to long-term care or acute care hospitals were very similar to the unadjusted ORs. Two trials with missing data^{29,34} were excluded from these analyses.

Random- vs fixed-effects model. We found minimal to no differences in summary ORs using random-effects or fixed-effects models. For example, the summary OR for mortality using the random-effects model was 0.83 (95% CI 0.75 to 0.91) and using the fixed-effects model was 0.83 (95% CI 0.76 to 0.90).

Discussion

Results of this meta-analysis of 19 randomized controlled trials, most of which were conducted in family practice settings, provide evidence that PPCO interventions substantially reduce risk of mortality and increase the likelihood of continuing to live in the community. Our findings suggest that PPCO interventions can make an important difference in

the lives of community-dwelling older people. The effect of PPCO interventions on mortality (OR 0.83, 95% CI 0.75 to 0.91) is comparable to the effect of pharmacotherapy for hypertension in elderly people (OR 0.84, 95% CI 0.75 to 0.94).³⁷ Using PPCO would prevent one death for every 36 older people targeted for intervention; one death would be prevented for every 63 hypertensive elderly people treated for 5 years with drug therapy.

Unlike evaluation of pharmacologic interventions, assessment of health service interventions usually involves evaluating a package of services or an intervention with multiple components. These interventions are sometimes referred to as “black box” interventions because the effect of their individual components is usually not evident. While this is challenging, it is typical of evaluations of health services interventions. In the absence of further research, how PPCO interventions specifically affect mortality remains somewhat speculative. Plausible explanations include the effect of early identification and management of risks and

comorbidity and greater attention to personal and health needs.

The findings of our meta-analysis are generally consistent with results of a recent meta-analysis of home visiting programs that offer health promotion and preventive care to older people.⁹ That study, which included six of the trials included in our meta-analysis and nine others not meeting our inclusion criteria, found that home visiting was associated with a 24% reduction in mortality among members of the general elderly population and a 28% reduction in mortality among frail older people. That study also found no significant reduction in admission to hospital (OR 0.95, 0.80 to 1.09), but, unlike ours, found a significant reduction in admission to long-term care of 35%.

The summary OR for the four Canadian trials (0.76) was comparable to the summary OR for all the studies included in this review, but was not statistically significant. This is not surprising, given that these four studies' sample sizes were generally small and that the four trials together accounted for only 4.6% of the total sample on which the summary estimate for mortality is based. The intervention is feasible in the Canadian health care system and the findings of this meta-analysis are highly relevant to policy development in primary care, particularly as it relates to care of older adults. The literature search described earlier was updated to the end of April 2004. We found no studies that met our eligibility criteria.

Our meta-analysis does not include unpublished studies or studies reported in languages other than English. The existence, direction, magnitude, and importance of bias resulting from exclusion of unpublished and non-English-language studies is controversial.³⁸⁻⁴⁰

We used a validated scale to determine the quality of studies.¹¹ Double blinding (one of the scale's criteria), however, was not applicable to this literature. Given the considerable variability in study quality, we included all studies in the meta-analysis and then did an adjusted analysis that included study quality as a covariate. Some of the randomized controlled trials included in this meta-analysis had noteworthy limitations. Only eight studies

described the random allocation procedure used. Many studies provided only a minimal description of the intervention itself.

Implications for future research. Some unanswered questions remain. It is possible that PPCO interventions, like geriatric evaluation and management interventions,^{41,42} result in more positive outcomes when targeting specific groups of frail elderly people. Patient characteristics, such as age and degree of functional impairment, might be useful selection criteria for such interventions.

The effect of PPCO on other important outcomes, such as physical functioning or activities of daily living, quality of life, cognitive or mental status, and cost-effectiveness, has not been adequately studied. Well designed and adequately powered intervention studies are clearly needed to address these unanswered questions.

Conclusion

Based on a meta-analysis of 19 randomized controlled trials, PPCO interventions appeared to reduce mortality by 17% among community-dwelling older people and to increase the likelihood of their continuing to live in the community by 23%. Our analyses do not indicate that PPCO interventions reduce admissions to long-term care or acute care hospitals. Results of this study have important implications for future research and health services planning. 

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Contributors

Dr Ploeg contributed substantially to concept and design of the study; to acquisition, analysis, and interpretation of

data; and to writing and revising the paper. Dr Feightner contributed to the conceptual framework and design of the study, to the literature review, and to manuscript revisions, and approved the final version of the paper. Drs Hutchison and Patterson contributed to the conceptual framework and design of the study, to data extraction, to literature evaluation, and to manuscript revisions, and approved the final version of the paper. Mr Siguouin contributed to data analysis and manuscript revisions and approved the final version of the paper. Ms Gauld assisted with the literature search; contributed to development of the data extraction form, data extraction, design and preparation of tables, and manuscript revisions; and approved the final version of the paper.

Competing interests

None declared

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