TITLE: Lifestyle Prescriptions: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

According to the World Health Organization (WHO), physical inactivity constitutes the fourth leading risk factor for death globally.[1] In 2008, nearly 1/3 of the world's adults aged 15 years or older were considered insufficiently active (men: 28%, women: 34%).[2] The reasons for this inactivity are manifold including a reduction in leisure time physical activity (PA), increases in occupational and domestic sedentary behavior, and increases in passive modes of transportation, along with the trend toward increasing urbanization and its associated environmental factors, some of which may serve to discourage PA.[2] In spite of these challenges, however, the argument for promoting PA as a population health strategy remains compelling since participation in regular PA has been reported to produce broad health benefits, including prevention or delay of chronic illnesses, such as diabetes and cardiovascular disease (CVD),[3] which can carry a high health and cost burden to the individual and to society. Because of accessibility and population served, primary health care clinics have often been targeted as a strategic channel through which to deliver various PA interventions.[4] These PA interventions can be wide-ranging in terms of scope, health human resource utilization, and cost.[4] Thus, identifying PA interventions that are effective, simple to administer, with low resource and cost implications potentially offers the greatest opportunity for uptake in the primary care setting. One such candidate PA intervention is a formal PA prescription issued by a prescriber (i.e., physician or nurse practitioner). Analogous to the way in which a medication is ordered, it is thought that a formal PA prescription might increase the likelihood of PA adoption by insufficiently active patients with minimal health human resource and cost implications to the clinic.

This review was therefore undertaken to assess the evidence for the clinical effectiveness of formal PA prescriptions issued by a physician or nurse practitioner for the primary prevention of chronic illness, specifically diabetes and cardiovascular disease, in otherwise healthy adults or in those with risk factors for the aforementioned diseases.

RESEARCH QUESTION

1. What is the clinical effectiveness of physical activity (PA) prescriptions issued by a recognized prescriber (i.e., physician or nurse practitioner) for the primary prevention of chronic illness in otherwise healthy adults or in those at risk for diabetes or CVD?

KEY FINDINGS

The evidence base for the use of formal physical activity (PA) prescription as a singular intervention to promote PA in a population at risk for chronic disease is limited and was judged to be of low methodological quality. Thus, it remains uncertain whether a PA prescription by itself can effectively promote increased PA.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and April 7, 2014.

Literature Search Strategy

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Healthy adults or adults at risk for diabetes or cardiovascular disease
Intervention	Formal prescription for exercise issued by either a physician or nurse practitioner
Comparator	No formal exercise prescription
Outcomes	Clinical effectiveness measured by change in: o Physical activity: by self-report or objective measure o Cardiorespiratory fitness (i.e., peak VO_2) o Clinical: body weight, blood pressure o Biomarkers: glucose, lipid profile o Quality of life o Symptoms (e.g., mood) • Adherence: by self-report
Study Designs	HTA/Systematic review/Meta-analysis, Randomized controlled trials, Non-randomized studies

Exclusion Criteria

Studies were excluded if the effect of exercise could not be isolated within the intervention (i.e., mixed interventions); the prescription was for supervised exercise (e.g., medically-supervised, physical medicine or rehabilitation program) or for conditions in which exercise was part of the standard of care in Canadian clinical practice; if the study population was mixed (i.e., primary and secondary prevention studied together); or if the exercise prescription was not issued by a recognized prescriber (i.e., physician or nurse practitioner).

Critical Appraisal of Individual Studies

Critical appraisal of the methodological quality of individual studies was performed using the Downs and Black instrument[5] for randomized and non-randomized studies. No systematic reviews were identified from the literature search that met the inclusion criteria for this review.

An annotated critical appraisal of the strengths and limitations of the individual included studies is provided in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 606 citations. After screening titles and abstracts, 559 articles were excluded and 47 potentially relevant articles were selected for full-text review. Seven relevant citations were identified from the grey literature. Of these 54 reports, 51 did not meet the inclusion criteria and were excluded, leaving a total of three relevant reports:[6-8] consisting one pre-post study,[6], one prospective cohort study,[7], and one randomized controlled trial.[8] No systematic reviews were identified that met the review's inclusion criteria. The study selection process is outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included studies are summarized below and detailed in Appendix 2.

Country of origin

A controlled, pre-post Canadian pilot study by Galaviz et al.[6] and two European studies – an uncontrolled pre-post study by Sabti et al.[7] from Switzerland and a RCT by Aittasalo et al.[8] from Finland – were identified for this review.

Population

The study by Galaviz et al.[6] included a convenience sample (n=35) of exclusively female patients aged between 25 and 45 years old with body mass index (BMI) of $\leq$ 35 kg/m^2, and identified by their Kingston, Ontario-based family physician as likely not meeting Canadian physical activity (PA) guidelines (i.e., 150 minutes weekly of moderate to vigorous aerobic PA[9]). Sabti et al.[7] enrolled insufficiently active patients (n=1,075) aged 16 to 65 years old, who were fluent in German, and who regularly attended primary care in urban or rural northwest Switzerland. ('Sufficient activity' was defined as 90 minutes of vigorous or 150 minutes of moderate intensity activity per week.[7]) Aittasalo et al.[8] studied patients aged 20 to 65 years old

attending primary care in Finland, with no perceived barriers to PA, but who engaged in moderate to vigorous PA of 30 minutes' duration less than 4 days per week.

Intervention

In Galaviz et al.,[6] the prescription-only (PO) group received brief (< 3 minutes) PA counseling + a PA prescription while the control group only received usual care (UC). Insufficiently active patients in the Sabti et al.[7] study initially received an educational pamphlet with tips for increasing PA and then a voucher one week later for two 30-minute PA counseling sessions with either a physiotherapist or physician. These insufficiently active patients also received feedback from their physician following completion of the study's screening PA questionnaire. In Aittasalo et al.,[8] patients randomized to the PREX intervention group received a PA prescription + PA counseling added to usual care.

Comparators

The comparator group in Galaviz et al.[6] received usual care only (i.e., no PA prescription or PA counseling). In the uncontrolled pre-post study by Sabti et al.,[7] the comparison was the same group over time, in which the change in PA among insufficiently active patients was compared after one year to baseline PA levels. A random sample of patients deemed sufficiently active at baseline was also drawn for descriptive comparison. In Aittasalo et al.,[8] there were two non-prescription (NPREX) comparator groups (MON, which included usual care + PA monitoring [i.e., five consecutive days using a pedometer + PA log], and CON, which included usual care only), but only one (CON) was relevant to this review due to MON's inclusion of additional activities (i.e., PA monitoring) that went beyond usual care and could be considered interventional.

Outcomes

Although not explicitly stated in their methods section, Galaviz et al.[6] examined the proportion of patients meeting Canadian PA recommendations and the associated weekly PA minutes accumulated after eight weeks of follow-up. In Sabti et al.[7] and Aittasalo et al.,[8] the primary outcome was the change in PA: after one year compared with baseline in the case of Sabti et al.[7] and after two and six months in the case of Aittasalo et al.[8] None of the studies assessed changes in cardiorespiratory fitness, body weight, blood pressure, biomarkers (i.e., blood glucose or lipoproteins), quality of life, symptom scores, or adherence (directly).

Summary of Critical Appraisal

Despite the Canadian context of the pre-post pilot study by Galaviz et al.,[6] the information it offers about the effectiveness of the PA interventions studied is limited owing to its small size (n=35 patients and 10 physicians), exclusive recruitment of female patients, , reliance on a single, self-report instrument for PA assessment, and its short duration (i.e., 8 weeks). The Swiss uncontrolled pre-post study by Sabti et al.,[7] which compared the change in PA from baseline to one year, involved a larger number of participating physicians (n=40) and patients (n=1,075) and a longer follow-up than the study by Galaviz et al.[6] In addition to leisure time PA, Sabti et al.[7] collected data about active (and passive) transportation.[6]. Unlike Galaviz et al.,[6]however, the lack of a comparator group by Sabti et al.[7] prevented drawing any meaningful conclusions from the data, as it is unclear how much of the effect can be attributed to the intervention and not to other factors that may have changed during the study period. Moreover,

it was unclear who administered the educational pamphlets and PA vouchers in the Sabti et al.[7] study or why there was a one-week delay between the issuance of these interventions. As with Galaviz et al.,[6] the change in PA was assessed by self-report, but it was unclear to what extent the self-report instrument was validated. Finally, change in PA was only assessed in patients for whom data was complete, thus omitting 11.5% of the patients for whom PA data was incomplete, which may lead to an overestimation of the true change with the intervention. The Finnish RCT by Aittasalo et al.[8] was the most well-conducted study of the three included studies. It included a clear schematic of the study design and well-described outcomes and statistical plan (including the handling of missing data); in addition, participating physicians were extensively trained on delivering the intervention prior to the launch of the trial. The study enrolled 265 patients who fell below a stated threshold for weekly PA (i.e., less than 4 days/week of moderate-intensity PA of 30 minutes' duration per session) according to the screening PA questionnaire; however, due to the trial's broad inclusion criteria and lack of information regarding the type of chronic illnesses prevalent in the study population, it is possible there were some secondary prevention patients with diabetes and/or cardiovascular disease included in this trial – a patient group, which was not part of this review's inclusion criteria. Since the duration of the trial was 6 months, it is possible that PA may be under- or over-estimated because of seasonal variation. As with the other two trials,[6,7] Aittasalo et al.[8] assessed PA through a self-report instrument, which had been modified for the study; however, the extent of its validation was unclear.

An annotated critical appraisal of the strengths and limitations of the individual included studies is provided in Appendix 3.

Summary of Findings

After eight weeks, Galaviz et al.[6] reported an increase from baseline in the proportion of women assigned the prescription-only (PO) intervention (25% to 58%) who met Canadian physical activity (PA) recommendations; PA did not change in the usual care (control) group. Sabti et al.[7] observed that after one year, patients who were inactive at baseline increased their total weekly minutes of both moderate (mean change: 58.8; 95% CI, 38.8 to 78.7) and vigorous-intensity (mean change: 34.6; 95% CI, 21.3 to 47.8) PA. Mean daily minutes spent walking (mean diff: 13.0; 95% CI, 3.7 to 22.2) and cycling (mean diff: 9.8; 95% CI, 5.3 to 14.3) also increased while time spent driving an automobile decreased (mean diff:–2.8; 95% CI, –10.6 to –5.1). Aittasalo et al.[8] found that patients assigned the PA prescription intervention (PREX) performed more weekly PA sessions of at least moderate-intensity than the control (CON) group at both 2 months (diff of means: 0.8; 95% CI, 0.1 to 1.5) and 6 months (diff of means: 0.9; 95% CI, 0.2 to 1.5) of follow-up; at these same time points, there were no statistically significant differences observed between groups in either the number or duration of overall weekly PA sessions, or in the duration of weekly PA sessions that were of at least moderate-intensity.

A tabular summary of findings from the individual included studies is provided in Appendix 4.

Limitations

The literature on the effectiveness of PA prescriptions as a stand-alone intervention would appear very limited while the quality of the studies included in this review was considered low overall. The assessment of physical activity, like nutrition, is challenged by limitations inherent in the self-report instruments typically employed along with the impracticality and often prohibitive

cost of using more objective measures to assess energy expenditure in large studies. Thus, a degree of caution must be exercised in interpreting the findings as it is likely that the observed effects are confounded by over-reporting, which may or may not be systematic depending on whether the study design was randomized or not. The three included studies limited their assessment of outcomes to short-term changes in PA; no information was provided on changes in cardiorespiratory fitness, body weight, blood pressure, or biomarkers (e.g., blood glucose, blood lipids) despite the connection of these outcomes with modifying an individual's risk for developing chronic disease. Finally, an examination of the extent of adherence and persistence with lifestyle interventions, including PA prescriptions, is a relevant outcome to consider, especially when it comes to translating research interventions into practice. In this literature review, there were no articles that investigated adherence analytically, that met the inclusion criteria. Nonetheless, several qualitative or descriptive articles[10-12] were screened, which the reader may wish to consult.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Physical inactivity is an important global public health and economic issue that may be expected to increase in prevalence with continued urbanization and modernization in the absence of effective countervailing interventions. Generally consistent with the recommendations from other countries, the Canadian Society for Exercise Physiology (CSEP) recommends that adults aged 18 to 64 years of age accumulate at least 150 minutes of moderate to vigorous intensity levels of aerobic physical activity (PA) per week in bouts lasting at least 10 minutes in order to reap health benefits.[9] One proposed strategy that may support increased PA is the issuance of a formal PA prescription by a recognized prescriber.

This review examined the clinical effectiveness of PA prescriptions issued by a physician or nurse practitioner for the primary prevention of chronic illness (i.e., diabetes or cardiovascular disease [CVD]) in otherwise healthy adults or in those at risk for diabetes or CVD. Three reports meeting the review's inclusion criteria were identified, which were considered to be of low methodological quality. The majority of the evidence base appeared to reside within mixed interventions (e.g., programs or systems of care) rather than examining a given intervention (e.g., PA prescription) in isolation. Moreover, the preponderance of multi-component interventions encountered in the literature seems to suggest a general research orientation toward more holistic than reductive approaches to lifestyle behavior intervention; these multi-component interventions inherently complicate an examination of the individual effectiveness of specific components. The study populations in many of the articles examining the effects of exercise and diet interventions are also often mixed,[13-18] in that the investigators included both people with and without disease, which is likely to be less informative when it comes to population and public health intervention planning than examining primary and secondary populations as separate entities.

The results of the three included studies, which comprised two non-RCTs and one RCT, were equivocal: the two non-RCTs reported increases in PA over time, but a number of limitations complicate the interpretation of findings. By comparison, the RCT showed that a PA prescription led to an increase in the number of weekly moderate-intensity PA sessions compared with control, but without corresponding change in the number of overall weekly PA sessions; no differences in the duration of weekly PA sessions were noted in either group. Considered in the context of the sparse evidence base and the included studies' limitations, it therefore remains uncertain whether a PA prescription by itself can effectively promote increased PA.

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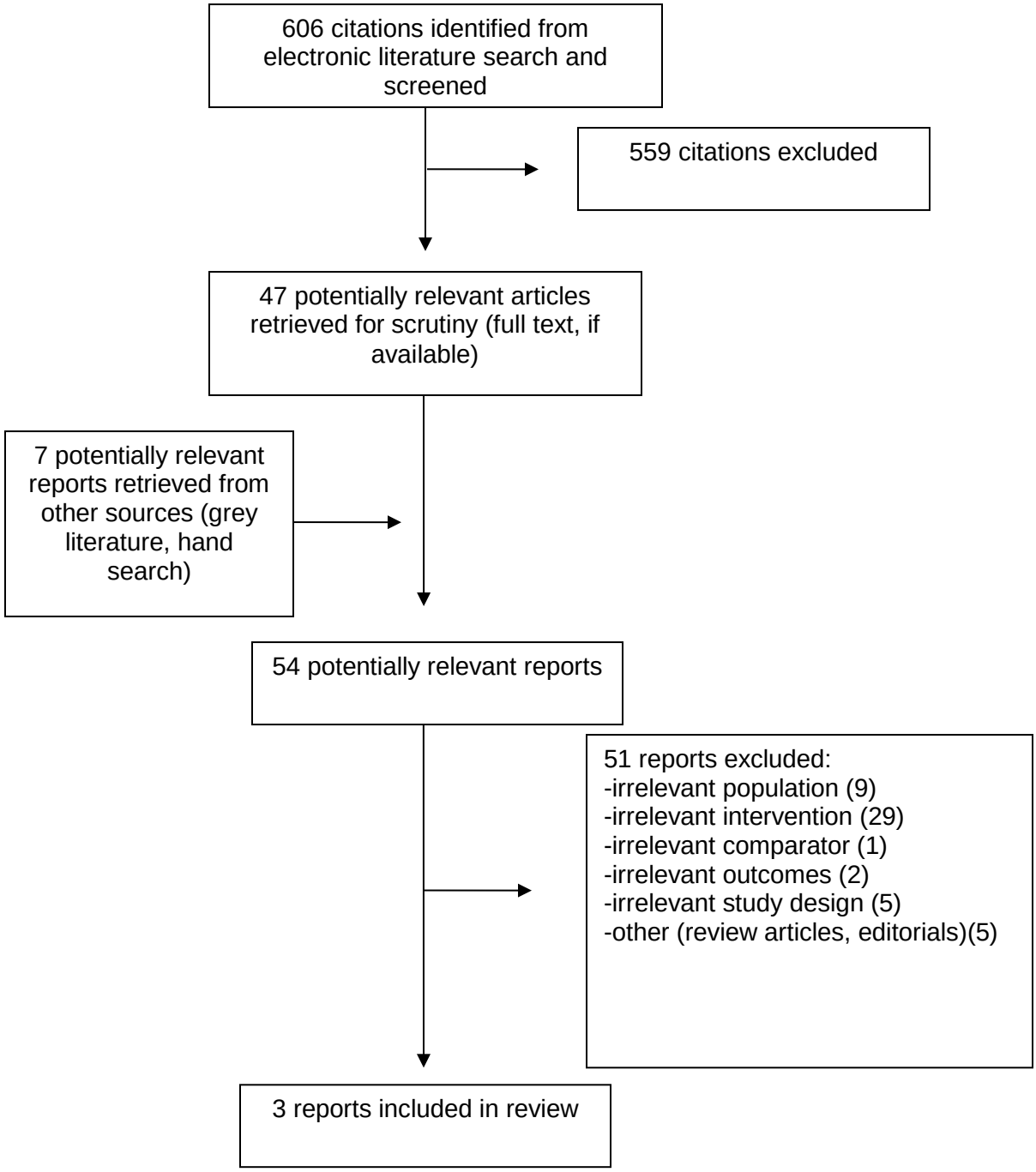
APPENDIX 1: Selection of Included Studies



Appendix 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design	Population	Intervention	Comparator	Outcomes
RCT/non-RCT					
Galaviz,[6] 2013, Canada	2 (pre-post) x 3 (treatment group) mixed design FPs randomized to: PP, PO, or UC; patients assigned to same condition as FP Duration: 8 weeks	Convenience sample: female patients (n=35) aged 25-45 y/o, BMI ≤35 kg/m^2, not meeting CAN PA guidelines Patients selected from a family medicine clinic located in mid-size Canadian city 10 FPs participated	PP group (n=12): PA Rx+ brief (< 3 min) PA counseling + referral to community program PO group (n=12):[a] PA Rx + brief (< 3 min) PA counseling	UC group (n=11): usual care only (no PA Rx or counseling)	Self-reported: total leisure-time PA; total weekly PA minutes
Sabti,[7] 2010, Switzerland	Pilot project; uncontrolled pre-post study + prospective cohort control group Duration: 1 year	Insufficiently active[b] patients (n=1,075) aged 16-65 y/o, able to communicate in German, and who regularly attended primary care in urban or rural NW SUI 40 PCPs participated	Insufficiently active[b] patients only: Over 2 weeks of a PA screening campaign: 1st week: educational pamphlet for increasing PA; 2nd week: voucher offered for 2 x 30-min counseling sessions with PT or MD. Consultation with MD following initial PA screening questionnaire.	Time: Baseline versus 12 months Cohort control: random sample of 'sufficiently active'[a] patients (n=601)	Self-reported: change in PA
Aittasalo,[8] 2006, Finland	RCT: Within each health care unit,	Patients (n=265) aged 20-65 y/o attending primary care in Finland with < 4 days/week of moderate-intensity	PREX: PA counseling + PA Rx + UC	NPREX: either MON or CON MON: UC + PA monitoring	Self-reported: change in PA (frequency, duration)

First Author, Publication Year, Country	Study Design	Population	Intervention	Comparator	Outcomes
	MDs randomized to PREX or NPREX; NPREX further split into UC only (CON) versus UC + PA monitoring (MON) All groups received UC. Duration: 6 months	PA of 30 min duration, no perceived obstacles for PA 67 PCPs were initially recruited; 45 PCPs actively participated in care		CON: UC only	

BMI=body mass index; **CAN**=Canadian; **CON**=control; **FP**=family physician; **MD**=physician; **MON**=monitoring; **NW**=northwest; **NPREX**=non-prescription group; **PA**=physical activity; **PCP**=primary care physician; **PP=**prescription plus; **PO**=prescription only; **PREX**=prescription group; **PT**=physiotherapist; **Rx**=prescription; **SUI**=Switzerland; **UC**=usual care; **y/o**=years old;

[a]Only the PO group was considered a relevant intervention for this review.

[b]Patients completed a PA screening questionnaire at baseline (pre-intervention) and one year later (post-intervention) to determine the amount of time spent performing moderate and vigorous intensity PA. Patients who performed either ≥90 minutes of vigorous PA or ≥150 minutes of moderate PA per week were considered sufficiently active.[7]

Appendix 3: Summary of Critical Appraisal

First Author, Publication Year, Country	Strengths	Limitations
RCT/non-RCT		
Galaviz,[6] 2013, Canada	• Prospective design • Clear description of study objective and interventions • Canadian population studied • Randomization of MDs to reduce risk of selection bias for a certain intervention group • MDs received training on intervention prior to study launch • PA counseling based on established model • Declarations of interest and sources of financial support both reported (in each case: none)	• Convenience sample: patients were selected by their MD for participation • Outcomes not explicitly described in methods section • Risk of selection bias: only 45% (10/22) of invited FPs and 11% (42/378) of eligible patients agreed to participate • Short follow-up (i.e., 8 weeks) • Pilot study, small sample size (n=35) • Only women studied. Literature review suggested gender disparities in physical activity adoption, so design may have been strengthened by a comparator group of men. • Unclear to what extent the modifications made to the GLTEQ for assessing total leisure-time PA (i.e., 10-min instead of 15-min bouts; addition of total minutes spent in each PA intensity) was validated. • Single self-report instrument (GLTEQ) for assessing PA
Sabti,[7] 2010, Switzerland	• Clear description of study objective • 'Sufficient' PA definition provided • High response rate (72%) for follow-up PA questionnaire; non-responder characteristics examined • Additional data collected on automobile driving as a marker of inactivity • Declarations of interest and sources of financial support both reported (in each case: none)	• Unclear whether it was the receptionist or HCP who issued the pamphlet and voucher to inactive patients, or why there was a one-week delay separating issuance of pamphlet and voucher to inactive patients. • Unclear to what extent the PA questionnaire – an amalgam of two surveys – was validated. • Unclear how additional questions about active commuting activities were handled analytically. • Few (16%) patients recalled receiving both a pamphlet and voucher or a voucher alone (3%) for PA counseling at baseline. • Change in PA was not evaluated in 11.5% of the follow-up population due to incomplete data from PA questionnaire. • Only within-group group differences from baseline were formally tested; no between-group statistical comparisons were performed against the

First Author, Publication Year, Country	Strengths	Limitations
		prospective control group.
Aittasalo,[8] 2006, Finland	• RCT design • Broad inclusion criteria • Clear description of outcomes and statistical plan (including handling of missing data) • Randomization of MDs to reduce risk of selection bias for a certain intervention group • MDs received extensive training on intervention prior to study launch • PA counseling based on established model • Interventions had been piloted before launching trial • PA definition provided (i.e., all daily PA excluding work) • High response rate to 2-month and 6-month follow-up PA questionnaire (80% and 77%, respectively) • Information about PA-related adverse events was collected	• PA assessed through self-report • Unclear to what extent the PA questionnaire – a modified version of an original – was validated. • Possible selection bias: despite broad inclusion criteria, only 54% (535/992) of screened patients deemed eligible for inclusion, of which 50% (265/535) consented to participate. • No information about chronic disease burden in study population: risk of mixed population of patients with and without diabetes or CVD • Observed physical activity levels potentially confounded by: o seasonal variation: 6-month intervention period ran from March to September o non-systematic external exercise referrals to other HCPs • Higher drop-out rate after 2 months of follow-up in control group (27%) vs intervention arms (17% and 16%).

CVD=cardiovascular disease; **FP=**family physician; **GLTEQ=**Godin Leisure-Time Exercise Questionnaire; **HCP**=health care professional; **MD**=physician; **PA**=physical activity; **RCT**=randomized controlled trial

Appendix 4: Summary of Findings

First Author, Publication Year, Country, Study Design	Main Study Findings	Authors' conclusions
RCT/non-RCT		
Galaviz,[6] 2013, Canada, pilot pre-post study	• The study population (n=35) had a mean age of 36 ± 5 y; only female patients were studied; no information was provided on body composition. After 8 weeks: • The proportion of patients meeting CAN PA recommendations increased in both PP (17% to 50%) and PO (25% to 58%) groups, but did not differ between groups. • PA scores and total weekly PA minutes increased in both PP and PO groups, but did not differ between groups. • PA did not change in the UC group.	*"…brief PA counseling and a prescription can be effective for improving short-term PA among women. Referring patients to the community program was no more effective than the counseling/prescription alone."* (p. 170)
Sabti,[7] 2010, Switzerland, uncontrolled pre-post study	• 1,216 (24.4%) of the 4,983 patients who completed a baseline PA screening questionnaire were considered inactive. • 1,075 (88.4%) of 1,216 inactive patients agreed to complete a follow-up PA questionnaire 1 year later; for comparative purposes, a random sample of 601 'active' patients from the original screened pool of 'active' (n=3,767) patients was also contacted for follow-up: o 73.9% (1213/1676) responded: 77.1% who were active at baseline and 72.2% who were inactive at baseline. o Respondents tended to be active at baseline and older (P <0.05). • The study population (i.e., inactive patients: n=1,075) had a mean age of 44.3±13.2 y; 45.3% were male and 47.6% were overweight with BMI > 25 kg/m^2. • After 1 year, patients who were inactive at baseline: o Increased their total weekly minutes of PA for both moderate (mean change: 58.8; 95% CI, 38.8 to 78.7) and vigorous (mean change: 34.6; 95% CI, 21.3 to 47.8) intensity PA. o Increased their mean daily minutes spent walking (mean diff: 13.0; 95% CI, 3.7 to 22.2) and cycling (mean diff: 9.8; 95% CI, 5.3 to 14.3)	• *"…receiving a voucher for a physical activity counselling session with a specially trained physician or physiotherapist or accepting a brochure with tips on how to increase physical activity was not associated with increased physical activity as reported at follow-up."* (p.283)

First Author, Publication Year, Country, Study Design	Main Study Findings	Authors' conclusions
	○ Reduced their mean daily minutes spent driving an automobile (mean diff: –2.8; 95% CI, –10.6 to –5.1), but the amount of time they spent using public transport did not change.	
Aittasalo,[8] 2006, Finland, RCT	• 24 (primary) health care units consisting of 45 MDs from the local catchment area took part in the study. • The study population (n=265) had a mean age of 47 ± 11 y; 24% were male; no information was provided on body composition. Chronic illness was reported in 86% of patients; no information was provided on type of chronic illness. • The number of weekly sessions of at least moderate intensity PA was higher in the PREX versus CON group at both 2 months (diff of means: 0.8; 95% CI, 0.1 to 1.5) and 6 months (diff of means: 0.9; 95% CI, 0.2 to 1.5) • After 2 and 6 months, there were no differences between PREX and CON groups in either the number or duration of overall weekly PA sessions, or in the duration of at least moderate intensity weekly PA sessions.	*"…physician-delivered PA prescription was able to increase the weekly frequency of patients'…at least moderate-intensity PA in both short and long-term."* (p.43-4)

CAN=Canadian; **CI**=confidence interval; **CON**=control; **FP=**family physician; **MON**=monitoring; **PA=**physical activity; **PP=**prescription plus; **PO=**prescription only; **PREX**=prescription; **Rx=**prescription; **UC=**usual care