Lifestyle Interventions to Prevent Cardiovascular Events After Stroke and Transient Ischemic Attack
Systematic Review and Meta-Analysis

Inger A. Deijle, MSc; Sander M. Van Schaik, MD; Erwin E.H. Van Wegen, PhD; Henry C. Weinstein, MD, PhD; Gert Kwakkel, PhD; Renske M. Van den Berg-Vos, MD, PhD

Background and Purpose—Patients with a transient ischemic attack or ischemic stroke have an increased risk of subsequent cardiovascular events. The purpose of this systematic review and meta-analysis was to determine whether lifestyle interventions focusing on behaviorally modifiable risk factors with or without an exercise program are effective in terms of (1) preventing recurrent cardiovascular events, (2) reducing mortality, and (3) improving modifiable risk factors associated with cardiovascular disease in patients after a transient ischemic attack or ischemic stroke.

Methods—For this systematic review and meta-analysis, we systematically searched PubMed, Embase, PsycInfo, and the Cochrane Library from the start of the database to May 7, 2015. Subgroup analyses were conducted to explore the influence of therapy-related factors.

Results—Twenty-two randomized controlled trials were identified with a total of 2574 patients. Pooling showed a significant reduction in systolic blood pressure by the lifestyle interventions applied, compared with usual care (mean difference, −3.6 mm Hg; 95% confidence interval, −5.6 to −1.6, I²=33%). No significant effect was found on cardiovascular events, mortality, diastolic blood pressure, or cholesterol. In the subgroup analyses, the trials with cardiovascular fitness interventions, trials with an intervention that lasted longer than 4 months, and interventions that used >3 behavior change techniques were more effective in reducing systolic blood pressure.

Conclusions—We found that lifestyle interventions are effective in lowering systolic blood pressure. About other end points, this systematic review found no effect of lifestyle interventions on cardiovascular event rate mortality, diastolic blood pressure, or total cholesterol. (Stroke. 2017;48:174-179. DOI: 10.1161/STROKEAHA.116.013794.)

Key Words: life style  secondary prevention  stroke

Patients with a transient ischemic attack (TIA) or ischemic stroke have an increased risk of recurrent stroke and other cardiovascular events.1,2 Risk factors for recurrent cardiovascular events can be classified into 3 major groups: (1) non-modifiable risk factors such as age, sex, and family history, (2) medically modifiable risk factors, which can be altered by medical interventions such as pharmacological therapy or surgical procedures, and (3) behaviorally modifiable risk factors, which can be modulated by changes in lifestyle factors such as physical inactivity and cigarette smoking.3 There is a solid body of evidence on the efficacy of secondary prevention measures that modify the medically modifiable risk factors in preventing recurrent stroke, coronary heart disease (CHD), and death.4,5 However, there is no solid evidence for interventions addressing behaviorally modifiable risk factors by lifestyle interventions in the literature, and it remains unclear which implementation strategy for lifestyle interventions is most effective.5,6 Lifestyle interventions are usually complex interventions with several interacting components,7 making it challenging to adequately describe and compare them in systematic reviews.

To date, 2 systematic reviews of lifestyle interventions to prevent recurrent stroke or cardiovascular events in patients after a TIA or ischemic stroke have been published.8,9 The first systematic review pooled 5 trials and found an overall significant increase in physical activity participation compared with usual care. No significant effects were reported for mortality, cardiovascular event rates, cholesterol, blood pressure, or cardiovascular risk factors. Unfortunately, this systematic review also included studies with other patients besides those with a TIA or ischemic stroke, such as patients with a lower limb amputation.10 The second review focused on nonpharmacological lifestyle interventions that included components from cardiac rehabilitation programs.9 One phase II trial was...
identified, in which patients were assigned to a 10-week exercise program or no intervention. A significant reduction in cardiac risk score based on age, resting blood pressure, smoking status, diabetic status, total cholesterol, and high-density lipoprotein levels was found in favor of the intervention group when compared with usual care.10 Both reviews stem from 2013 (including trials up to 2012), thereafter several new studies of lifestyle interventions with or without an exercise program have been published.

The primary objective of the current systematic review and meta-analysis of randomized controlled trials (RCTs) was to determine whether lifestyle interventions focusing on behaviorally modifiable risk factors with or without an exercise program are effective in terms of (1) preventing recurrent cardiovascular events, (2) reducing mortality, and (3) improving modifiable risk factors associated with cardiovascular disease in patients after a TIA or ischemic stroke. The secondary objective was to explore the influence of therapy-related factors such as timing of intervention, intensity, total duration, and the use of behavior change techniques.

Materials and Methods
This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.11 We searched PubMed, Embase, PsycInfo, and the Cochrane Library from the start of the database to May 7, 2015. Definitions, study selection, and data extraction are available in the Materials and Methods in the online-only Data Supplement. A protocol for this systematic review was not published.

Quality Assessment
Two reviewers (I.D. and S.S.) independently assessed the risk of bias, solving disagreements in a consensus meeting. The quality of RCTs was assessed using the checklist developed by the Cochrane Collaboration, which evaluates the presence of potential selection bias, performance bias, detection bias, attrition, and reporting bias.12

Quantitative Analysis
Meta-analyses were performed for each intervention for which at least 2 RCTs with comparable outcomes were identified. Statistical analysis was performed using RevMan 2014 version 5.3 and was conducted according to the Cochrane handbook for systematic reviews of interventions.13 See the Materials and Methods in the online-only Data Supplement for detailed description of the quantitative analysis. The separate effects of behavior change interventions, cardiovascular fitness interventions, and interventions involving both components were pooled for meta-analysis. Subsequently, a subgroup analysis investigated the effects of therapy-related factors. In addition, linear regression analyses were used to determine associations between individual mean differences (MD), on the one hand, and timing of the intervention, total duration, intensity, and the use of behavior change techniques, on the other. All analyses used 2-sided test and an α value of 0.05, regression coefficients with their corresponding 95% confidence interval (CI) were calculated.

Subgroup Analyses
The cutoff points for the subgroup analyses were the median values for the studies reporting the following variables: (1) timing of the intervention (within 3 months after onset of TIA or ischemic stroke or >3 months after onset of TIA or ischemic stroke), (2) total duration (≤4 versus >4 months), (3) intensity (≤8 versus >8 contact moments); and (4) number of different behavior change techniques (≤3 versus >3). These analyses are based on comparison of the subgroup effect and their CIs. Nonoverlap of the CIs indicated statistical significance.13

Results

Study Identification
The study selection process is summarized in Figure 1. The search in electronic databases yielded a total of 19,148 titles. After reviewing titles and abstracts, 37 full-text articles were retrieved for possible inclusion, 15 studies were subsequently excluded. The excluded articles can be found in the Result in the online-only Data Supplement.

Study Description
Twenty-two RCTs met the inclusion criteria with a total of 2,574 patients: 12 trials used a behavior change intervention (n=552),14–25 5 trials used a cardiovascular fitness intervention (n=1,800),26–30 and 5 trials used a combined intervention (n=222).10,31–34 Table I in the online-only Data Supplement summarizes the included studies.

Risk of Bias Assessment
Table II in the online-only Data Supplement illustrated the result of the risk of bias assessment according to the Cochrane guidelines.12 Nine studies had a low risk,10,16,18,24–26,32–34 8 had a moderate risk,14,17,21,23,27–29,31 and 5 had a high risk of bias.15,19–21,30 Three of the 5 studies with a high risk of bias had outcome measures that were not suitable for pooling, whereas 2 of the
5 provided suitable data for pooling but were excluded in the meta-analysis because of high risk of bias.\textsuperscript{15,19}

**Therapy-Related Factors**

The timing of the intervention ranged from 2 weeks to >1 year after the TIA or ischemic stroke.\textsuperscript{10,32} Intensity ranged from no patient contact moments (2 interventions provided only a personalized secondary prevention plan to the patient’s general practitioner)\textsuperscript{15,21} to 72 contact moments.\textsuperscript{28} Duration of the intervention ranged from 1 contact moment\textsuperscript{21} to a 24-month intervention.\textsuperscript{26} The number of behavior change techniques used ranged from 1\textsuperscript{21,25,27,29,30} to 7 described techniques.\textsuperscript{33} The main therapy-related factors are summarized in Table I in the online-only Data Supplement.

**Effect of Interventions**

**Meta-Analysis**

**Cardiovascular Event Rate and Mortality**

Figure 2 shows cardiovascular event rates of 506 patients after pooling\textsuperscript{24,26,31,33} Lifestyle interventions were found to have a heterogeneous nonsignificant effect on the risk ratio when compared with usual care (risk ratio, 0.79; 95% CI, 0.30–2.06; F=59% random-effect). Figure 3 shows the risk of death summarized >5 trials (n=1492 patients).\textsuperscript{16,24–26,33} No significant difference was found in the risk ratio of death (risk ratio, 1.16; 95% CI, 0.82–1.63; F=0% fixed-effect). Subgroup analyses showed no significant difference between the effects on the number of cardiovascular events (including mortality) between therapies focusing on behavior change interventions, cardiovascular fitness interventions, and combined interventions.

**Blood Pressure**

Figure 4.1 shows data of 650 patients from 10 studies.\textsuperscript{10,14,18,24,27,29,31–34} Pooling showed a significant reduction in systolic blood pressure (SBP) by the lifestyle interventions applied compared with usual care (baseline to postintervention were pooled for a total of 648 patients from 8 studies).\textsuperscript{10,14,34} A nonsignificant heterogeneous MD in SBP reduction was found (MD, −0.2 mm Hg; 95% CI, −6.8 to −0.5; F=38% fixed-effect and MD −2.2 mm Hg; 95% CI, −8.2 to 3.8; F=52% random-effect). We found no significant effect of trials that used ≤8 patient contacts for their intervention and trials that used >8 patient contacts (MD, 1.0 mm Hg; 95% CI, −4.5 to 6.5; F=0% fixed-effect and MD −4.3 mm Hg; 95% CI, −6.5 to −2.2; F=33% fixed-effect, respectively).

In linear regression analysis, a significant negative association is found in both the number of contact moments and SBP (regression coefficient, −2.5; 95% CI, −4.3 to −0.6) and number of behavior change techniques applied and SBP (regression coefficient, −0.5; 95% CI, −0.5 to −0.03).

Changes in diastolic blood pressure (DBP) from baseline to postintervention were pooled for a total of 648 patients from 8 studies.\textsuperscript{10,14,18,24,27,29,31–34} A nonsignificant heterogeneous MD in DBP reduction was found (MD, −0.2 mm Hg; 95% CI, −2.2 to 1.9; F=55% random-effect). Figure I in the online-only Data Supplement shows the meta-analysis for DBP.

**Cholesterol**

Three trials (n=126) were pooled, showing a nonsignificant MD for total cholesterol level (MD=0.09 mmol/L; 95% CI, −0.30 to 0.48; F=0% fixed-effect).\textsuperscript{10,14,34}

**Physical Activity and Cardiorespiratory Fitness**

Thirteen studies reported physical activity as an outcome measure: 8 studies (n=874) using a behavior change intervention,\textsuperscript{10,16,17,19–21} 2 studies (n=427) using a cardiovascular fitness intervention,\textsuperscript{26,28} and 3 studies (n=154) using a combined intervention.\textsuperscript{32,34} The heterogeneity of the outcome measures prevented pooling. The outcome measures of these studies varied from change in self-reported minutes spent on exercise per week\textsuperscript{24} to maintaining an exercise program.\textsuperscript{19} Six interventions led to a significant increase of the physical activity level\textsuperscript{19,22,23,34} whereas 6 interventions yielded no significant changes in the

The subgroup analyses showed a significant effect of treatment duration, a difference in effect was found in favor of trials with interventions that lasted longer than 4 months compared with those lasting ≤4 months (MD, −2.6 mm Hg; 95% CI, −4.7 to −0.4, F=0% fixed-effect and MD, −10.1; 95% CI, −15.4 to −4.8; F=0% fixed-effect, respectively). For the use of behavior change techniques, a significant effect was also found in favor of trials with interventions that used 3 behavior change techniques or less and those using >3 behavior change techniques (MD, −2.6 mm Hg; 95% CI, −4.7 to −0.4; F=0% fixed-effect and MD, −10.1 mm Hg; 95% CI, −15.4 to −4.8; F=0% fixed-effect, respectively). With regards to the timing of the treatment, no difference in effect was found between trials starting within 3 months or trials starting after 3 months (MD, −3.7 mm Hg; 95% CI, −6.8 to −0.5; F=38% fixed-effect and MD −2.2 mm Hg; 95% CI, −8.2 to 3.8; F=52% random-effect). We found no significant effect of trials that started <3 and >4 months (MD, −2.6 mm Hg; 95% CI, −9.0 to −1.3; F=19% fixed-effect and MD, −5.3 mm Hg; 95% CI, −9.0 to −1.6; F=46% fixed-effect, respectively).
level of physical activity, and one study did not report the outcome of the measure. Four studies (n=170) found a significant increase in cardiorespiratory fitness in the intervention group as measured by VO2max or maximal oxygen uptake. One study (n=28) used a 6-minute walking test to measure cardiorespiratory fitness and reported a significant and clinically relevant change in the intervention group (412±178 to 472±196 m versus 459±116 to 484±122 m in the control group; P<0.01; minimal clinically important difference, 29 m).

**Discussion**

The main finding of this meta-analysis was a significant 3.6-mmHg reduction in SBP by lifestyle interventions compared with usual care. In the subgroup analyses, the trials with a cardiovascular fitness intervention and a combined intervention showed a significant reduction in SBP, whereas trials with a behavior change intervention showed no significant effect. About other end points, this systematic review found no effect of lifestyle interventions on cardiovascular events, mortality, DBP, or total cholesterol. The lack of positive effects for these end points may be explained by the fact that the study samples were small and the follow-up was short, with a median duration of 5.5 months.

The secondary aim of the present review was to investigate which therapy-related factors have an impact on the intervention effect. Our subgroup analyses indicated that interventions involving a cardiovascular fitness program result in a significant reduction in SBP. This may be explained by the fact that endurance training decreases blood pressure by reducing systemic vascular resistance. Furthermore, our subgroup analyses showed that trials with an intervention that lasted longer than 4 months and interventions that used >3 behavior change techniques were more effective in reducing SBP. In this analysis, the same trials lasted longer than 4 months and used >3 behavior change techniques, this makes it difficult to

### Figure 3.
Risk ratio with 95% confidence interval (CI) estimates for death (lifestyle interventions vs usual care) among patients with transient ischemic attack or ischemic stroke. M–H indicates Mantel–Haenszel statistic.

### Figure 4.
Meta-analysis and subgroup analysis for mean difference in systolic blood pressure with 95% confidence interval (CI; lifestyle interventions vs usual care) among patients with transient ischemic attack or ischemic stroke. IV indicates inverse variance.
to disentangle whether the effect modification is because of duration of the number of behavior change techniques. Linear regression analyses suggested that there is a positive association between the number of contact moments and number of behavior change techniques used and change in SBP.

Blood pressure is the most consistent and powerful predictor of stroke, in both primary and secondary prevention. It is debatable whether the 3.6-mm Hg reduction in SBP found in this systematic review and meta-analysis is clinically relevant. The PROGRESS trial (The Perindopril Protection Against Recurrent Stroke Study) found no difference in the risk of stroke or major vascular events in the group treated by perindopril alone and for whom the SBP was on average 5 mm Hg lower than in the placebo group. Despite this uncertainty on clinical relevance, it is at least remarkable that it was achieved by offering patients lifestyle interventions and not prescribing antihypertensive drugs or by performing a strictly pharmacologically based intervention. Furthermore, it might be relevant from an epidemiological perspective, as it presumably reduces the cardiovascular event rates in the population of TIA and patients with ischemic stroke. Therefore, as a complement to antihypertensive drugs, lifestyle interventions may be effective in lowering blood pressure and reducing recurrent TIA or stroke rates.

The results on SBP in our systematic review are consistent with those of other systematic reviews, which investigated the effect of exercise-based cardiac rehabilitation programs in patients with CHD. For example, the review by Taylor et al reported a significant 3.2-mm Hg decrease in SBP in patients with CHD, but no significant difference in DBP after an exercise-based cardiac rehabilitation program was observed. In contrast to our systematic review, Taylor et al found a significant reduction in all-cause mortality (odds ratio, 0.8; 95% CI, 0.68–0.93), cardiac mortality (OR, 0.74; 95% CI, 0.61–0.96), and cholesterol levels (MD, −0.37 mmol/L; 95% CI, −0.63 to −0.11). However, the total number of patients in their meta-analyses was larger than that in the current review (8432 versus 1492), and it is not clear whether mortality rates are comparable between patients with CHD and patients with stroke.

Parallels between comorbidities and risk factors in stroke and CHD suggest that a cardiac rehabilitation model of care may provide patients after a TIA or ischemic stroke with much needed improvement in both secondary prevention and cardiorespiratory fitness. The latter is important because evidence from several trials consistently shows a significant decline in cardiorespiratory fitness and physical functioning after both TIA and stroke. However, more knowledge is needed about the similarities and differences between patients after a TIA or stroke and CHD, about both psychosocial characteristics (cognition, depression, anxiety, and fatigue) and physical performance.

The present review has some limitations. First, despite the inclusion criteria, there was substantial heterogeneity in the interventions applied, with regards to content, intensity, and duration, especially for the behavior change interventions. This is a well-known difficulty when comparing complex lifestyle interventions, where heterogeneity of intervention content and mode of delivery is likely to be large. Second, because no biologically determined cutoff points are known, the cutoff points in the subgroup analyses for the timing of the intervention, its intensity, patient contacts, duration, and use of behavior change techniques were determined using the median value. Third, because of our language restrictions, we may have missed trials published in other languages than English and studies published in non-peer-reviewed journals. Fourth, because of the large variety in outcome measures, a limited number of studies were suitable for pooling. Finally, the limited number of trials that we found preclude the use of funnel plots to determine small-study effects.

We suggest that future high-quality RCTs investigating the effects of lifestyle interventions on preventing cardiovascular events, mortality, and modifiable risk factors should meet the following criteria: (1) complete description of all therapy-related characteristics of the intervention; the timing of the intervention, the intensity, the duration of the intervention, and the use of behavior change techniques, with the aim to improve replicability and comparability between studies; (2) the lifestyle intervention should preferably consist of >8 contact moments, distributed over a treatment period of at least 4 months; (3) the lifestyle intervention should use >3 behavior techniques; (4) the lifestyle intervention should include a guided cardiovascular fitness intervention with behavior change interventions, i.e., guidance on how to achieve and maintain an active lifestyle, in combination with guidance on medication adherence, smoking cessation, alcohol intake, and diet; (5) use a theoretical framework in developing lifestyle interventions. Because changing lifestyles is known to be difficult, the development of a lifestyle intervention can be facilitated by taking into account all factors that might influence the change in health behavior. These factors include cognitive factors, such as self-efficacy, knowledge, and attitude, as well as environmental factors. A theoretical framework, such as the Transtheoretical Model, can be used as an approach to understand these factors.

Obviously, a large phase III trial of high methodological quality is needed to answer the question whether lifestyle interventions are effective in preventing recurrent cardiovascular events, reducing mortality, and influencing modifiable risk factors.

Disclosures

None.

References


Lifestyle Interventions to Prevent Cardiovascular Events After Stroke and Transient Ischemic Attack: Systematic Review and Meta-Analysis

Stroke. 2017;48:174-179; originally published online December 6, 2016; doi: 10.1161/STROKEAHA.116.013794

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/1/174

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/12/21/STROKEAHA.116.013794.DC1
SUPPLEMENTAL MATERIAL

Effects of lifestyle interventions to prevent recurrent cardiovascular events after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis.

Inger A. Deijle¹, MSc; Sander M. Van Schaijk², MD; Erwin E.H. Van Wegen³, PhD; Henry C. Weinstein², MD PhD; Gert Kwakkel⁴, PhD; Renske M. Van den Berg-Vos², MD PhD

¹ Department of Physical Therapy, OLVG, Amsterdam, The Netherlands
² Department of Neurology, OLVG, West, Amsterdam, The Netherlands
³ Department of Rehabilitation Medicine, Move Research Institute Amsterdam, VU Medical Center, Amsterdam, The Netherlands.
⁴ Department of Rehabilitation Medicine, Move Research Institute Amsterdam, VU Medical Center and Amsterdam Rehabilitation Research Center, Reade Center for Rehabilitation and Rheumatology, Amsterdam, Netherlands

Corresponding author:
R.M. Van den Berg-Vos, M.D., Ph.D.
Department of Neurology, OLVG, West
Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands
e-mail: r.vandenberg-vos@olvg.nl
tel: +31 205108780, fax: +31 206837198
TABLE OF CONTENTS

1. Material and methods
   a. Definitions
   b. Study selection
   c. Data extraction
   d. Quantitative analysis
2. Results, excluded studies
3. Table I: Included studies and therapy related factors
4. Table II: Risk of bias assessment
5. Figure I: Meta-analysis and subgroup analysis for mean difference in diastolic blood pressure
6. Literature search strategy
7. References supplemental material
1. MATERIALS AND METHODS

1a. Definitions
In accordance with the definition used by the American Heart Association/American Stroke Association (AHA/ASA), transient ischemic attack (TIA) was defined as “a transient episode of neurological dysfunction caused by focal brain, or retinal ischemia, without acute infarction”.

Ischemic stroke was defined as “an episode of neurological dysfunction caused by focal cerebral, or retinal infarction”.

Minor stroke was not defined in a consensus definition, but it is generally assumed that minor stroke is “an ischemic stroke with a short-term good functional outcome”.

A study was considered an RCT when “the individuals followed in the trial were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation”.

At this moment there is no consensus on the classification of lifestyle interventions. In this systematic review we use the following three categories: 1) behavior change interventions, 2) cardiovascular fitness interventions or 3) a combination of both of these. Behavior change interventions aim to change health behavior of patients, and thereby the behaviorally modifiable risk factors.

Behavior change interventions can be defined as “coordinated sets of activities designed to change specified behavior patterns”.

They address one or more of the following aspects: physical inactivity, overweight or obesity, cigarette smoking, heavy alcohol use, hypertension, lipid profile, medication adherence.

There are various forms of behavior change interventions. Widely used is education to improve knowledge about health behavior. Other forms are counseling programs to improve self-management or self-regulation, and specific techniques such as motivational interviewing.

Cardiovascular fitness interventions are defined as “interventions with the aim to improve the level of physical activity and/or cardiorespiratory fitness and to influence modifiable risk factors, for example blood pressure and cholesterol”.

The third type lifestyle intervention is a combination of a behavior change intervention and a cardiovascular fitness intervention. In clinical practice the combination of exercise training with psychosocial education is implemented at large scale in so called cardiac rehabilitation programs for patients with CHD, which are effective in reducing total and cardiovascular mortality and hospital admissions.

In the subgroup analysis we explored if components of lifestyle interventions were significantly associated with the prevention of recurrent cardiovascular events, reduced mortality and improved modifiable risk factors. For this purpose the following therapy related factors are explored: start of intervention relative to TIA or ischemic stroke onset, intensity, total duration, use of behavior change techniques. The start of intervention was described as the time from onset TIA or ischemic stroke until start of the intervention, and was described in months. The intensity was defined as the amount of patient contacts, which can be done face-to-face, via telephone or online. The total duration of the intervention was described in months. To describe the use of behavior change techniques in this review, we used the CALO-RE taxonomy from Michie et al.

This taxonomy comprises 40 behavior change techniques, and can be used to identify potential active ingredients in studies.

1b. Study selection
We searched Pubmed, Embase, PsycInfo and the Cochrane Library from the start of the database up until May 7, 2015. An experienced librarian assisted in developing the search strategy. The search was performed with an extensive string, including American/English spelling and singular/plural terms. Keywords focused on TIA, stroke and synonyms, risk reduction behavior, lifestyle interventions, exercise therapy, secondary prevention, diet, smoking cessation and health knowledge (supplement 1). Studies were included if they met the following inclusion criteria: 1) were Randomized Controlled Trials (RCT), 2) involved...
patients older than 18 years, with a history of TIA or ischemic stroke, 3) compared the effect of lifestyle interventions with usual care or no intervention, and 4) aimed to improve cardiovascular risk profile, recurrence of cardiovascular events and mortality for TIA or ischemic stroke survivors. The types of interventions included were behavior change interventions, cardiovascular fitness interventions or a combination of both. Studies were included when they used one of the following outcomes measures: risk of recurrent cardiovascular disease (CHD, recurrent TIA or ischemic strokes, vascular death), blood pressure (resting systolic and DBP), lipid profiles (total cholesterol, low and high density lipoprotein cholesterol), physical activity measures (questionnaires and activity monitors), cardiorespiratory fitness measured by maximal exercise capacity test (VO2max) or by submaximal cycling, or walking capacity tests such as the 6 minutes walking distance (6MWD), body weight (body mass index, waist circumference), dietary behavior, alcohol use, and tobacco use. Studies with pharmacological interventions alone are excluded in this systematic review.

1c. Data extraction
One review author (I.D) conducted the first search on titles based on the inclusion and exclusion criteria. Two review authors scanned the extracted titles and abstracts independently (I.D and S.S), they discussed differences and reached consensus. In the next stage, the same two authors scanned full-text articles independently and they discussed their selection for inclusion and reached consensus. Recorded data variables were trial name, year of publication, country of origin, patient characteristics, start of intervention, intensity, total duration, mode of delivery, use of behavior change techniques, setting, health care provider, use of theoretical framework, outcome measures, duration of follow-up, and number of patients for each group. Corresponding authors were contacted if data was unclear or missing.

1d. Quantitative analysis
The data required for meta-analyses of continuous data were numbers of patients, outcome measures, means, and standard deviations (SD) of post-intervention scores on outcome measures for both the experimental and control group means. For continuous data, mean differences (MD) with 95% confidence intervals (CIs) were calculated if the studies used the same instrument to measure an outcome (for example blood pressure). If studies used different instruments (for example different maximal exercise capacity tests), the standardized mean difference (SMD) with 95% CI was calculated. When the standard deviation (SD) was missing, standard error or 95% CI was used to calculate the SD. For dichotomous data, risk ratios (RR) with 95% CIs were calculated using the Mantel-Haenszel statistical method. We assume in our meta-analysis that the effects of lifestyle interventions have the same quantity or impact on stroke patients irrespective of age, gender, ethnicity or having risk factors for stroke. With that, we theoretically assumed that the effects of lifestyle interventions are the more or less the same among different stroke phenotypes and chose for a fixed-effects model and subsequently, verified the model by using the $I^2$ ratio test with a cut off of 50% or less. In case of significant heterogeneity, a random effects model was used in line with the guidelines of the Cochrane Handbook (version 5.1.0). We assessed the possibility of publication bias by evaluating a funnel plot of the trial mean differences for asymmetry, which can result from the nonpublication of small trials with negative results. When a protocol of an individual study was available, the outcomes in the protocol and the published report was compared.
2. RESULTS, EXCLUDED STUDIES
15 studies were subsequently excluded: two studies because the reported outcome was other than the aforementioned outcome measure,\textsuperscript{12,13} six studies were no RCTs\textsuperscript{14-19} and seven studies included other patients than patients with TIA or ischemic stroke.\textsuperscript{20-26}
### 3. Table I: Included studies and therapy related factors

<table>
<thead>
<tr>
<th>Author, year of publication, country</th>
<th>Patient characteristics (patient condition, N, age, % men)</th>
<th>Description intervention</th>
<th>Follow-up</th>
<th>Start of intervention</th>
<th>Intervention: intensity &amp; total duration</th>
<th>Behavior change techniques*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adie et al. (2010) UK</td>
<td>Minor stroke or TIA N=56 Age= 74.7 Men = 54%</td>
<td>Intervention group: telephone follow-up and educational material. Control group: usual care.</td>
<td>6 months</td>
<td>&lt; 1 month after minor stroke/TIA</td>
<td>Intensity: 4 patient contacts Total duration: 4 months</td>
<td>2. Provide information on consequences of behavior to the individual 27. Use of follow up prompts 37. Motivational interviewing</td>
</tr>
<tr>
<td>Allen et al. (2002) USA</td>
<td>Ischemic stroke or TIA N=96 Age= 70.5 Men = 44.5 %</td>
<td>Intervention group: an individual treatment plan for patients and GP. Control group: usual care.</td>
<td>3 months</td>
<td>&lt; 1 month post discharge</td>
<td>Intensity: 0 patient contacts Total duration: 3 months</td>
<td>2. Provide information on consequences of behavior to the individual 27. Use of follow up prompts</td>
</tr>
<tr>
<td>Allen et al. (2009) USA</td>
<td>Ischemic stroke N= 360 Age= 68.5 Men= 50%</td>
<td>Intervention group: home visit with standard education. Personalized health record and periodic phone calls. A copy of the care plans was send to GP. Control group: usual care + written patient summary.</td>
<td>6 months</td>
<td>&lt; 2 months post discharge</td>
<td>Intensity: 12 patient contacts Total duration: 6 months</td>
<td>2. Provide information on consequences of behavior to the individual 16. Prompt self-monitoring of behavior 27. Use of follow up prompts</td>
</tr>
<tr>
<td>Damush et al. (2011) USA</td>
<td>Ischemic stroke N= 63 Age= 65.7 Men= 98.4%</td>
<td>Intervention group: stroke self-management program with a 2 weekly telephone sessions, and at 4.5 months a booster call. Control group: written patient education materials, placebo telephone calls.</td>
<td>6 months</td>
<td>&lt; 1 month post discharge</td>
<td>Intensity: 7 patient contacts Total duration: 4.5 months</td>
<td>2. Provide information on consequences of behavior to the individual 5. Goal setting (behavior) 16. Self-monitoring of behavior 18. Prompting focus on past success 27. Use of follow up prompts 28. Facilitate social comparison</td>
</tr>
<tr>
<td>Ellis et al. (2005) UK</td>
<td>Stroke or TIA N=205 Age=65.1 Men=53%</td>
<td>Intervention group: individual advice on lifestyle changes and written information. Control group: usual care.</td>
<td>5 months</td>
<td>&lt; 3 months after stroke/TIA</td>
<td>Intensity: 3 patient contacts Total duration: 3 months</td>
<td>2. Provide information on consequences of behavior to the individual 27. Use of follow up prompts</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Stroke Type</td>
<td>N</td>
<td>Age (mean)</td>
<td>Men (%)</td>
<td>Intervention Group</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Flemming et al. (2013) USA</td>
<td>USA</td>
<td>Atherosclerotic ischemic stroke</td>
<td>42</td>
<td>70.1</td>
<td>58.5</td>
<td>Intervention group: a physician-directed nurse-case-management program.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilham et al. (2010) UK</td>
<td>UK</td>
<td>Minor stroke or TIA</td>
<td>52</td>
<td>68.3</td>
<td>71</td>
<td>Intervention group: information from the nurse practitioner. Two times telephone support to discuss progress.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green et al. (2007) Canada</td>
<td>Canada</td>
<td>Stroke</td>
<td>200</td>
<td>66.8</td>
<td>58.5</td>
<td>Intervention group: nurse-mediated motivational counseling intervention and a 3-hour lifestyle group class.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. (2013) Republic of Korea</td>
<td>Republic of Korea</td>
<td>Ischemic stroke</td>
<td>36</td>
<td>65.6 years</td>
<td>63.9</td>
<td>Intervention group: web-based stoke education program.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maasland et al. (2007) The Netherlands</td>
<td>Netherlands</td>
<td>Minor stroke or TIA</td>
<td>65</td>
<td>64</td>
<td>60</td>
<td>Intervention group: information from the physician, health information by an individualized multimedia computer program, printed summary.</td>
</tr>
<tr>
<td>Study</td>
<td>Number of Participants</td>
<td>Age</td>
<td>Gender</td>
<td>Intervention</td>
<td>Control Group</td>
<td>Duration</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>--------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>McManus et al. (2007)</td>
<td>Stroke or TIA</td>
<td>N= 102</td>
<td>Age= unclear</td>
<td>Intervention group: three times written and verbal about lifestyle. Risk factors were assessed at each visit. Control group: usual care.</td>
<td>43 months</td>
<td>&lt; 3 months after stroke</td>
</tr>
<tr>
<td>Wolfe et al. (2010)</td>
<td>Stroke</td>
<td>N= 523</td>
<td>Age= 21.29% &gt;80 years Men= 53%</td>
<td>Intervention group: Tailored evidence-based management advice was provided on paper to patients, their GP, and caregivers. At 3 and 6 months keeping well plan was modified. Control group: usual care.</td>
<td>8 months</td>
<td>&lt; 6 months after stroke</td>
</tr>
<tr>
<td>Exercise interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boysen et al. (2009)</td>
<td>Ischemic stroke</td>
<td>N= 314</td>
<td>Age= 69.5 Men=31.5 %</td>
<td>Intervention group: repeated individual instruction to improve physical activity. Follow-up visits with repeated instruction and readjustment physical activity plan. Control group: patients receive information on the possible benefits of physical benefits but no specific instruction.</td>
<td>24 months</td>
<td>&lt; 90 days after stroke</td>
</tr>
<tr>
<td>Potempa et al. (1995)</td>
<td>Hemiplegic stroke</td>
<td>N= 42</td>
<td>Age= 43 to 72 years Men= 54.8 %</td>
<td>Intervention group: patients received exercise training on an adapted cycle ergometer. Control group: 10 weeks program of passive range of motion exercise.</td>
<td>2.5 months</td>
<td>&lt; 6 months after stroke</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Stroke</td>
<td>Participants</td>
<td>Intervention Details</td>
<td>Duration</td>
<td>Intensity Details</td>
<td>Total Contacts</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Rimmer et al. (2009) USA</td>
<td>Unilateral ischemic stroke</td>
<td>N=55, Age= 59.6 years, Men= 40%</td>
<td>Intervention group 1: moderate intensity, shorter duration exercise. Intervention group 2: low-intensity, longer duration exercise. Control group: conventional therapeutic exercise.</td>
<td>3.5 months</td>
<td>Intensity: MISD group: 24 patient contacts LILD group: 24 patient contacts Total duration: 3.5 months</td>
<td>21. Provide instruction on how to perform the behavior</td>
</tr>
<tr>
<td>Shaughnessy et al. (2012)</td>
<td>Ischemic stroke</td>
<td>N= 113, Age= 64.4, Men= 44 %</td>
<td>Intervention group: treadmill training focused on an ultimate goal of engaging the patients in three 40-minute exercise sessions weekly. Control group: stretching program.</td>
<td>6 months</td>
<td>Intensity: 72 patient contacts Total duration: 6 months</td>
<td>5. Goal setting (behavior) 21. Provide instruction on how to perform the behavior</td>
</tr>
<tr>
<td>Toledano-Zarhi et al. (2011) Israel</td>
<td>Minor stroke</td>
<td>N= 28, Age= 65, Men= 75 %</td>
<td>Intervention group: exercise program on a treadmill, bike machine. Group practice for strength, flexibility and coordination performances. A home exercise booklet was provided. Control group: instructions in home practice to achieve strength and flexibility and continue with normal routine.</td>
<td>2.5 months</td>
<td>Intensity: 12 patient contacts Total duration: 2.5 months</td>
<td>21. Provide instruction on how to perform the behavior</td>
</tr>
<tr>
<td>Faulker et al. (2013) New Zealand</td>
<td>TIA and nondisabling stroke (NDS)</td>
<td>N=60</td>
<td>Intervention group: exercise and education sessions.</td>
<td>2 months</td>
<td>Intensity: 32 patient contacts Total duration: 8 weeks</td>
<td>2. Provide information on consequences of behavior to the individual</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Intervention</td>
<td>Control Group</td>
<td>Timeframe</td>
<td>Intensity</td>
<td>Duration</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
</tbody>
</table>
| Kirk et al. (2014) UK        | TIA and minor stroke  | Intervention group: cardiac rehabilitation program consisting of weekly exercise and education classes | Control group: usual care.                  | 6 months  | < 1 month | 8 weeks   | 21. Provide instruction on how to perform the behavior  
27. Use of follow up prompts                                                                 |
| Kono et al. (2013) Japan     | Mild ischemic stroke  | Intervention group: exercise training, salt restriction and nutrition advice. | Control group: 3 times lifestyle modification + usual medical care. | 35 months | Acute mild non cardio embolic ischemic stroke | 6 months   | 2. Provide information on consequences of behavior to the individual  
10. Prompt review of behavior goals  
17. Prompt self-monitoring of behavior  
21. Provide instruction on how to perform the behavior  
26. Prompt practice  
27. Use of follow up prompts                                                                 |
| Lennon et al. (2008) Ireland | Ischemic stroke       | Intervention group: 30-minute cycle ergometer exercise.                      | Control group: usual care.                  | 2.5 months| > 1 year after stroke | 2.5 months | 19. Provide feedback on performance  
21. Provide instruction on how to perform the behavior  
36. Stress management / emotional control training                                                                 |

*The behavior change techniques are numbered according to the Taxonomy from Michie 2011.*
4. **Table II: Risk of bias assessment** (Cochrane handbook) (yes, no, unclear)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of personnel and outcome assessors</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other risk of bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behaviour change interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adie et al. (2010)</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Allen et al. (2002)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Allen et al. (2009)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Damush et al. (2011)</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ellis et al. (2005)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Flemming et al. (2013)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Gillham et al. (2010)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Green et al. (2007)</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Kim et al. (2013)</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Maasland et al. (2007)</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>McManus et al. (2007)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Wolfe et al. (2010)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Exercise interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boysen et al. (2009)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Potempa et al. (1995)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rimmer et al. (2009)</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Shaughnessy et al. (2012)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Toledano-Zarbi et al. (2011)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Combined interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boss &amp; van Schaik et al. (2014)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Faulkner et al. (2013)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Kirk et al. (2014) UK</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Kono et al. (2013)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Lennon et al. (2008)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
</tbody>
</table>
5. **Figure I**: Meta-analysis and subgroup analysis for mean difference in diastolic blood pressure with 95% confidence interval (CI) (lifestyle interventions vs usual care) among patients with TIA or ischemic stroke.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adie 2010</td>
<td>75.7</td>
<td>10.1</td>
<td>29</td>
<td>72.1</td>
<td>12.1</td>
<td>27</td>
<td>8.0%</td>
<td>3.60 [-22.6, 9.46]</td>
</tr>
<tr>
<td>Bass &amp; Schalk 2014</td>
<td>71.1</td>
<td>10.1</td>
<td>10</td>
<td>75</td>
<td>8.3</td>
<td>10</td>
<td>5.1%</td>
<td>-4.00 [-12.10, 4.10]</td>
</tr>
<tr>
<td>Ellis 2009</td>
<td>81.3</td>
<td>17.8</td>
<td>94</td>
<td>78.8</td>
<td>22.7</td>
<td>98</td>
<td>8.2%</td>
<td>2.50 [-5.16, 8.26]</td>
</tr>
<tr>
<td>Faulkner 2013</td>
<td>80.0</td>
<td>9</td>
<td>96</td>
<td>79.1</td>
<td>10</td>
<td>12</td>
<td>10.7%</td>
<td>1.00 [-5.54, 5.54]</td>
</tr>
<tr>
<td>Kirk 2014</td>
<td>74.7</td>
<td>8.7</td>
<td>12</td>
<td>75</td>
<td>7.9</td>
<td>12</td>
<td>6.8%</td>
<td>-0.30 [-6.95, 6.35]</td>
</tr>
<tr>
<td>Kono 2013</td>
<td>72.9</td>
<td>9.5</td>
<td>35</td>
<td>80.7</td>
<td>10.7</td>
<td>35</td>
<td>10.2%</td>
<td>-7.80 [-12.54, -3.06]</td>
</tr>
<tr>
<td>Lenner 2008</td>
<td>81.4</td>
<td>8.4</td>
<td>23</td>
<td>82</td>
<td>9</td>
<td>23</td>
<td>9.6%</td>
<td>-0.60 [-5.63, 4.43]</td>
</tr>
<tr>
<td>McManus 2007</td>
<td>74.3</td>
<td>10.3</td>
<td>49</td>
<td>74</td>
<td>12.2</td>
<td>53</td>
<td>11.1%</td>
<td>0.00 [-4.37, 4.37]</td>
</tr>
<tr>
<td>Potempa 1995</td>
<td>78.4</td>
<td>2.1</td>
<td>19</td>
<td>76.4</td>
<td>1.6</td>
<td>23</td>
<td>20.4%</td>
<td>2.00 [0.85, 3.15]</td>
</tr>
<tr>
<td>Teledano Zarri 2011</td>
<td>78.4</td>
<td>5.5</td>
<td>14</td>
<td>79.2</td>
<td>7.3</td>
<td>14</td>
<td>10.1%</td>
<td>-0.80 [-5.59, 3.99]</td>
</tr>
</tbody>
</table>

Total (95% CI) 321 327 100.0% -0.15 [-2.23, 1.93]

Heterogeneity: Tau^2 = 5.19; Chi^2 = 19.78, df = 9 (P = 0.02); I^2 = 55%
Test for overall effect: Z = 0.14 (P = 0.89)

IV: Inverse Variance; SD: standard deviation.

6. **LITERATURE SEARCH STRATEGY**


7. REFERENCES ONLINE-ONLY DATA SUPPLEMENT


