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An assessment on the methodological differences between economic evaluations on lifestyle and drug interventions: A systematic review

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Abstract

Introduction An economic evaluation provides information to investigate whether an intervention is a good use of society's resources; it assists policy makers to make an optimal decision for different interventions in various settings. Lifestyle and drug intervention are often implemented for primary preventive purposes in many diseases, among other cardiovascular diseases. Based on the Dutch guideline for cardiovascular risk management, in primary prevention, physical activity and diet as lifestyle intervention and statins as drug intervention are advised for people with low to moderate high CVD risks. Studies have shown favourable outcomes in the cost-effectiveness of these two interventions. However, based on the nature of these two interventions, it is interesting to have more insight on how these economic evaluations are conducted and observe if differences exist between studies on lifestyle and drug interventions. The purpose of this systematic review is to assess potential disparities in the methodology between the cost-effectiveness studies on drug treatment (i.e. statins) and lifestyle interventions (i.e. a combination of physical activity and diet advice) for primary prevention of cardiovascular diseases. Further, this study is also interested in potential relationships between different factors (e.g. time horizon, funding source, incremental cost-effectiveness ratios and etc.) and to what extent these associations hold for these two interventions.

Method A systematic literature search has been performed through different databases including Medline, Scopus and NHS-EED-HTA. Data is extracted from twelve economic evaluations that were eligible according to the inclusion criteria. Further, study characteristics and outcomes are analysed between studies on the two interventions. The quality of these studies is compared based on the BMJ quality checklist. Potential associations between different types of study characteristics, study characteristics and outcomes are assessed within/across studies. From these associations, it is examined to what extent these hold for both interventions.

Results In general, minor systematic differences are found on the methodology between lifestyle and drug interventions. When comparing the study characteristics between these two interventions, little methodological disparities were observed on the types of population, the comparators, perspective, intervention time, type of costs included and time horizon. Further, when comparing the relationships between study characteristics, two points are observed. First, it seems that the study perspective does not correspond to the costs that should be included (societal costs were often not included). Second, a relation is found between the choice of discount rate and the country that these studies were conducted in. On these two observations, no systematic differences are found between the two types of interventions. This also holds for the assessment on potential relationships between study characteristics and their outcomes. However, a general issue is observed within these studies on both interventions. Most of the twelve reviewed economic evaluations had a transparency problem in the documentation of their methodologies such as a lack of explanation in approaches, stating the time horizon, intervention period, range and variables of sensitivity analysis, choice of comparator and discount rate.

Conclusion Lacking transparency and comparability between studies in documentation on the methodology of economic evolutions could reduce optimal policy making. Future research should put more focus on the investigations in the field of methodology of economic evaluations in general, quality of guidelines and checklists.

1. Introduction

An economic evaluation provides information to investigate whether an intervention is a good use of society's limited resources; in addition it offers analysts and policy-makers the opportunity to compare different programs in terms of a common metric such as quality of life.[1−3] The Wanless reports recommended that in order to create an efficient approach to improve health of the population, a generation of evidence on cost-effectiveness of public health strategies is needed.[4−5] Methods for economic evaluation of health care interventions have mostly focused on clinical interventions such as drugs, medical devices and procedures.[1,6] During the past years, evaluating the cost-effectiveness of public health interventions has gained greater attention among researchers. However, compared to clinical interventions, economic evaluations on public health interventions are scarce. Furthermore, applying economic evaluations on public health interventions faces difficulties given their broad nature.[6−7] Because of this, methodological challenges such as attribution of effects, measuring and valuing outcomes, equity considerations, identifying intersectoral costs and consequences are often recognized when conducting economic evaluations in this field.[6]

Previously published literature on the transparency, methodology or consistency among different economic evaluations did not systematically investigate potential discrepancies among different types of interventions.[8−11] However, one could suspect that there could be substantial disparities in the methods of performing an economic evaluation, which should be taken into account to provide more reliable information for policy making. Based on previous results on the difficulties of economic evaluations on public health interventions,[6−7] it is questioned whether there are substantial differences in the methodology of conducting an economic evaluation among different types of interventions. Especially, the difference in methodology between drug and public health intervention is quite interesting because of their great difference in nature. Previous researches on both types of interventions have concluded that different factors such as funding source, modelling, time horizon and discount factor could affect the outcome such as cost-effectiveness ratio.[8−11] For instance, a study have concluded that the factor funding source could have an effect on the ICERs because of different study incentives.[9] However, these studies only reviewed economic evaluations on the interventions separately. None of the studies have evaluated both drug and public health interventions. Characteristics of public health interventions are quite different compared to drug interventions. An explanation could be the broad nature of public health interventions. Public health interventions are implemented to gain societal rather than individual wealth; it observes costs and effects from a broader perspective. However, drug interventions often focus on individual health gain and observe the costs from a health payer perspective[1].[12] This indicates

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[1]Health payer perspective: budget relevant costs and effects are taking into account while conducting an economic evaluation (e.g. treatment costs, drug costs).

that because of the difference in their study objectives, methodology could be different between these two interventions. Based on the previous findings and the nature of these two different interventions, it is interesting to have more insight on how these economic evaluations are conducted and observe if difference exists between studies on lifestyle and drug interventions.

As an interest of the Dutch public health institute in public health forecasting and in order to facilitate policy making, the purpose of this study is to gain more insight on the potential differences in the methodology between cost-effectiveness studies on preventive drug treatment and public health interventions. Besides this, this study is also interested in potential relationships between different factors (e.g. time horizon, funding source, Incremental cost-effectiveness ratios and etc.) and to what extent these associations hold for these two different types of interventions. For these aims, a systematic review has been conducted. Primary preventive interventions for cardiovascular diseases (CVDs) are chosen because of a large burden of disease worldwide.[13] Further, CVD is associated with numerous risk factors such as physical inactivity, overweight and smoking causing higher risk for developing cardiovascular diseases such as diabetes mellitus 2 and hypertension.[14] Lifestyle (public health intervention) and drug interventions are used in both primary and secondary preventive programs for reducing the risk of CVD and both have shown effectiveness to a certain extent. Based on the Dutch guideline for cardiovascular risk management, in primary prevention, lifestyle interventions (physical activity and diet) and drug interventions (statin) are advised.[15] For this reason, this systematic review focuses on physical activity and diet interventions compared to statin treatment in the primary prevention of CVD for a population with low to moderate high CVD risk and no previous history of CVD as an example of assessing potential methodological differences.

2. Methods

Different databases were used in order to identify all relevant studies. Medline, CRD (Centre for review and dissemination) and Scopus were used for locating the articles by inserting all possible combinations of meSH terms (medical subject heading) and keywords. CRD contains three categories of different databases: NHS-EED, HTA and DARE; only the NHS-EED and the HTA databases were used to search for economic evaluations. The search terms were categorized into six sub-groups: cost-effectiveness studies, cardiovascular diseases, prevention, diet, physical activity programs and statin treatment. Within each sub-group, meSH and synonym terms were made and combined. The searches for the articles on lifestyle and drug treatment were performed separately. First, a combination of meSH terms was constructed to find cost-effectiveness studies of physical activity and diet interventions, i.e. combining the sub-groups cost-effectiveness studies, cardiovascular diseases, prevention and diet and physical activity. Second, the cost-effectiveness studies of statins were found by combining the terms cost-effectiveness studies, cardiovascular diseases, prevention and statins (see appendix for complete search terms).

Data extraction and criteria From our perspective, this systematic review includes all relevant articles that have been published until 2011. The search initially identified 1,150 articles (see figure

1). Duplicated articles (N=279) have been removed if the articles contained the same keywords, title and authors. After duplication, title and abstract were read followed by global and full review of the articles. From the 871 studies for title and abstract reading, exclusion is based on three categories. First, the studies those were not suitable according to the PICO model (N=283). The PICO model (population, intervention, comparator and outcome) is used to define the inclusion criteria. The eligible population for this review is defined as individuals with a low to moderate high CVD risk[2]; individuals with an elevated cholesterol level, hypertension or obesity are included because they are assumed to have a low to moderate high CVD risk. Studies were only selected when their comparator of the intervention was placebo (for the economic evaluations on drug interventions), standard care[3] or no care (for the economic evaluations on lifestyle interventions). Outcome measures were based on the standards of cost-utility (quality adjusted life years (QALY)) and cost-effectiveness (life expectancy (LE), life years gained (LYG), or life years saved (LYS) and CVD events prevented). Second, only full economic evaluations (i.e. cost effectiveness studies and cost utility studies) were selected. Cost of illness studies, effect studies, protocols and reviews have been excluded (N=451). Third, studies that were not published in English have been excluded (N=47). The remaining studies were eligible for the following step: global reviewing (N=90) based on the PICO model. A majority of studies did not only focus on a population with low to moderate high CVD risk, but on patients with previous CVD history; these were assumed to be secondary prevention and excluded. (N=30). Furthermore, many studies did not assess cost-effectiveness of physical activity and diet interventions or statin treatment separately, but in a combination with other interventions such as screening. Thus, these studies were also excluded (N=21). Further, some studies did not compare the new intervention with placebo, standard care or no treatment but with other interventions (N=13). Finally, a study that paid attention to intermediate outcomes such as amount of cholesterol reduced was excluded (N=1). After the exclusion by global reviewing, 25 identified articles were included for the final step: a full review. Studies were excluded based on an unsuitable population (N=3), intervention (N=7) and comparator (N=4). With the remaining eleven studies that were chosen for this review, a systematic search through the reference lists was conducted to find potential articles that were eligible for inclusion. One study was found through this search and has been added to the total.[16]

This systematic review included twelve economic evaluations, i.e., four economic evaluations on lifestyle interventions[8,17−19] and eight on drug interventions.[16,20−26] From these twelve articles, data were extracted on both study characteristics and on the results of the economic evaluations. The general study characteristics consisted of the target population, type of intervention, comparator, study design, short and long-term effectiveness, type of costs, discount rates of costs/effects, price year, study perspective, source of funding, intervention period, time horizon and country in which the study was conducted. Information about the study results was collected, including the incremental costs and effects, incremental cost-effectiveness ratio (ICERs), sensitivity analysis and conclusions as stated by the authors. When the results were reported incomplete, calculations were made in this review for incremental costs, effects and ICERs based on standard methodology of calculating the ICERs.[27] In addition to presenting the

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[2]An individual with a 10-year risk of fatal CVD (cardiovascular diseases) risk above 5% and no previous history of CVD.
[3]Normal procedures aimed at primary prevention on CVD at the general practitioner.

key findings in their local currency and price year, costs were converted to Euro values of that time. The methods to convert the outcomes emerged from the advice of the Organization for Economic Co-operation and Development and then recalculated with the price index of 2010 of statistics Netherlands in order to facilitate comparisons across studies.[28−29]

Along with data extraction, the quality of articles was evaluated by using the BMJ quality checklist.[30] This checklist contains 35 questions related to the study design, data collection and their analysis in results. The possible answers for the referees when assessing the quality on each question of the BMJ checklist are: item adequately addressed, item inadequately addressed, not stated, not applicable, referred to reference and item partially addressed. A percentage of fulfilment for every question was calculated separately for the four included economic evaluations on lifestyle interventions and for the eight economic evaluations on drug interventions. When calculating the percentages, item adequately addressed (100%), item inadequately addressed (0%), item partially addressed (50%), referred to reference (r = 50%) and not applicable (NA = 0%) were used to calculate the average fulfilment rate.

Finally, potential relationships between study characteristics, characteristics and outcomes are examined within/across studies. From these potential relationships, it is observed to what extent these differ between the two interventions. The potential associations are investigated and divided into two categories: the potential relationships between different types of study characteristics (i.e. study population, type of intervention, comparator, study design, short/long-term effectiveness measure, type of costs, discount rates, price year, perspective, funding source, intervention period, time horizon and country) and the relationship between study characteristics and outcomes (outcomes are i.e. incremental costs/effects, incremental cost-effectiveness ratio, type of sensitivity analysis, results of the sensitivity analysis and author's conclusion).

The data extraction and quality assessment were performed in association with two peer reviewers (Laura Burgers and Heleen Hamberg). Consensus meetings were arranged to sort out ambiguities and discrepancies in opinions.
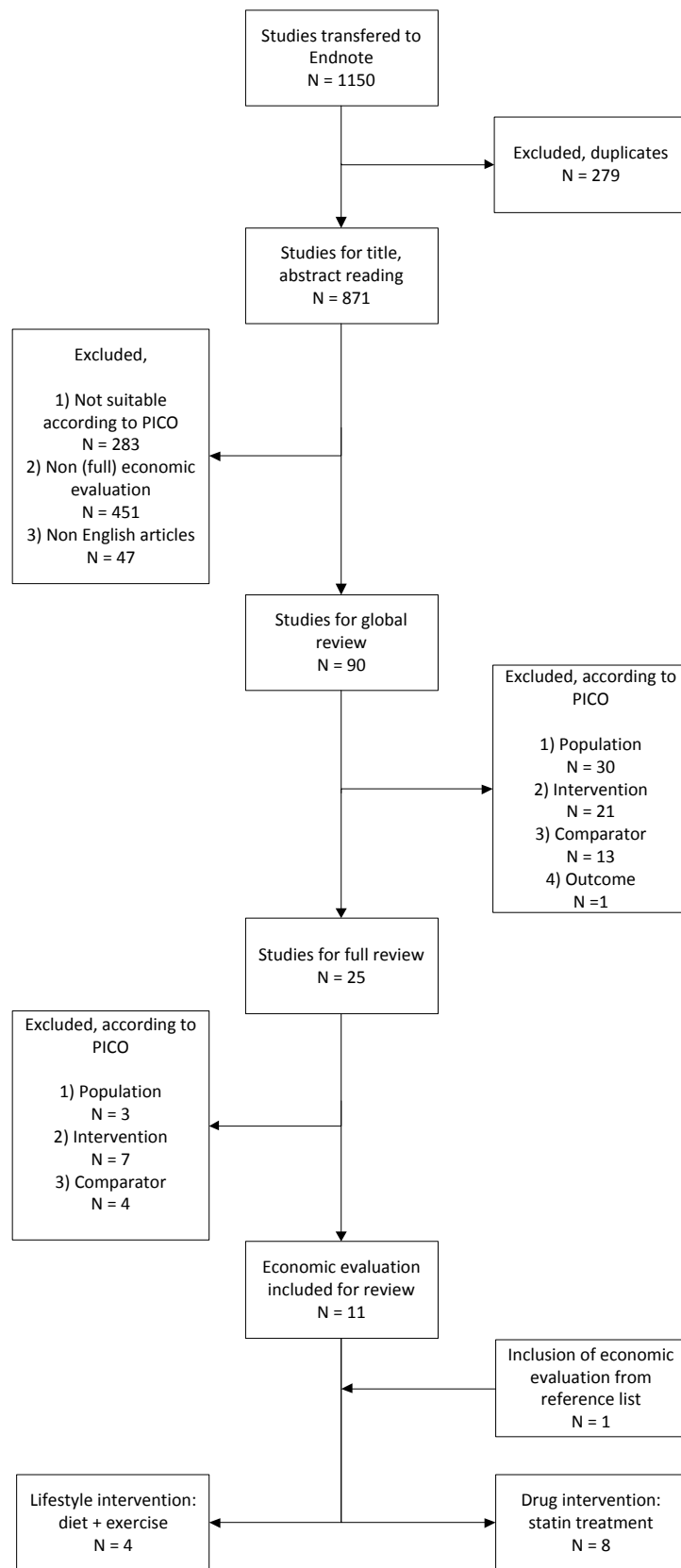
Figure 1: Flow chart of review selection from databases: Medline, Scopus and NHS-EED-HTA

3. Results

Altogether, four economic evaluations on lifestyle and eight on drug interventions in the primary prevention of cardiovascular diseases were eligible for final review. In the following, study characteristics and outcomes of these studies will first be listed, analyzed and compared between the two interventions. Furthermore, key findings that resulted from the BMJ quality checklist are investigated. The final section (3.4) shows the potential relationships between factors within/across studies. From these relationships, it is assessed to what extent these differ between the two interventions.

3.1 Study characteristics of the selected articles

Potential differences on study characteristics between economic evaluations on physical activity and diet intervention (lifestyle intervention) and statin treatment (drug treatment) are described detailed in the following (see Tables 1-6 in appendix).

The age of the *target population* within the reviewed economic evaluations on physical activity and diet interventions had a great range, i.e. a general age public between 18 to 85 years old. On the contrary, the included economic evaluations on statin treatment had a different range, which indicates that the starting age begins later than lifestyle interventions (above 30 years old). Except from one, this study did not select on age but only on the risk factor.[26] Within all studies, there was no selection between men or women as population inclusion criteria. One study on statin treatment excluded women in their target population.[23]

The reviewed *interventions* on physical activity and diet varied from simple provision of information about behavior changes to active participation, which involved counseling for diet behavior and physical activity. For statin treatment, studies included one or more types of statin treatment with different doses.

As *comparator*, economic evaluations on physical activity and diet interventions mainly used standard care; one study compared its lifestyle intervention with no intervention. Economic evaluations on statin treatment used placebo[16,20,22,26] or no treatment[21,23-25] as comparator. From the placebo-studies, some older studies did not directly state this comparator in their study,[16,20] but only referred to the underlying clinical trials.

The used *study design* was mainly a decision analytic modeling (DAM). From the studies on physical activity and drug interventions, three of four have chosen for using decision analytic modeling[8,18-19] and for studies on statin treatment, six of the eight studies have chosen for DAM.[20-21,23-26] Within the studies that have chosen for modeling, markov model was mainly conducted. The most of the studies have conducted their modeling study based on their population group, only one study has chosen for a hypothetical cohort in conducting their modeling study.[18] Next to this, few economic evaluations on both types of interventions used a so-called piggy-back design (i.e. based on a randomized controlled trial.[17,19,22,26] In overall, no clear differences were found between lifestyle and statin studies on their choice of study design.

The *type of economic evaluation* conducted varied very little between lifestyle and drug intervention. Within the physical activity and diet intervention studies, two have conducted a cost-utility analysis

with the effect measure QALY;[17−18] one performed a cost-effectiveness analysis by using LYG as effect measure[8] and another combined a cost-effectiveness and a cost-utility analysis.[19] Within the economic evaluations of statin treatment, four studies have conducted a cost-effectiveness study by using respectively LE or LYS and number of CVD events and procedure avoided as effect measure,[16,20,22−23] two conducted a cost-utility analysis[24−25] and two studies combined cost-effectiveness and a utility analysis.[21,26] On both types of intervention a trend was discovered between the type of economic evaluation conducted and the time line. It was observed in this review that before the year 2000 a majority were cost-effectiveness studies and after 2000, more cost-utility studies were reported.

The stated *study perspective* differed between lifestyle and statin treatment. The included economic evaluations on physical activity and diet interventions all had a societal perspective[4] or a combination of a societal and a health-payer perspective. On the contrary, for statin therapy, only two out of seven studies had a societal perspective. The rest were mainly conducted from a health-payer perspective.

The *types of costs* that were included were primarily direct medical costs such as treatment and drug cost. Only 50% of the economic evaluations on physical activity and diet interventions[8,19] have considered indirect costs such as productivity losses in their calculations. This is quite contradictory when observing the study perspectives of these studies, because all studies on physical activity and diet interventions stated to use a societal perspective. The same applies to the studies on statin treatment; all studies only considered direct medical costs. However, two studies[20,24] did not adhere to a societal perspective.

A great variety was found between the *source of funding* of studies on physical activity/diet interventions and statin treatment. It is observed that foundations or government funding all included economic evaluations on lifestyle interventions. On the contrary, almost all studies on drug interventions were funded by the pharmaceutical industry. Based on the results of the previous literature, it is concluded that when studies are funded by the pharmaceuticals, the study outcomes may be affected because of financial incentives.[9] In section 3.4.2, comparison between the funding and outcomes will be made to observe whether there is a relationship between these two factors and potential differences between lifestyle and drug interventions.

The *time horizon* was not always directly stated in studies on both interventions. The time horizons were mostly derived from the model that was used or the time length of the randomized controlled trials (RCT). It was observed that 50% of the studies on physical activity and diet interventions,[8,18] and almost all studies on statins were based on a lifetime time horizon (circa 90%).[16,20−21,23−26] The intervention period differed between economic evaluations on physical activity and diet interventions and statin treatment. The studies on lifestyle interventions had a fixed intervention period ranging between one to three years; all studies on statin treatment had a lifetime intervention period since statin treatment need to be used lifelong. Further, three out of the four lifestyle studies had a specific range of intervention period but a longer time horizon.[8,17−18] Controversially, intervention period and time horizons were aligned in the studies on drug treatments.

Most selected studies were conducted in developed *countries*. Three out of the four economic

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[4]Societal perspective: All relevant costs and effects of the intervention will be taking into account when conducting an economic evaluation (e.g. costs by informal care, productivity costs).

evaluations on physical activity and diet interventions were conducted in Europe (one from Switzerland, two from Sweden)[8,17−18] and one economic evaluation was conducted in Australia.[19] The countries that conducted studies on statin treatment were evenly spread in the region of North America (two from the US and two from Canada),[16,20,23,26] Asia (one from Japan and one from Korea)[21,24] and Europe (one from Ireland and one multi-national study within seven European countries).[25]

3.2 Study outcomes of the selected articles

Both interventions on physical activity and diet and statin treatment in the primary prevention of cardiovascular diseases could be regarded as cost-effective comparing to no intervention, placebo or standard care depending on the selected age, CVD risk, gender, discount rate, study perspective and threshold value (see Tables 7,9,11,12 in appendix). Because of these discrepancies, it is a challenge to compare ICERs between these studies. In general, it is observed that the range of the cost-effectiveness ratio is never located in the southeast quadrant of the cost-effectiveness plane since the costs of the new intervention are always higher than the cost of the comparator with a minimum gain of effects. The ICERs of physical activity and diet intervention ranged from €40 to €10 million per QALY/LYG and for statin treatment from approximately €10.000 to €540.000 per QALY/LYS/LYG. In economic evaluations on both types of interventions, ICERs were estimated for different scenarios.

It is observed that the ICERs of the studies on lifestyle intervention slightly decrease by time (see Figure 2). At in Figure 2, the red triangles and blue squares represent the change in ICERs and the intervals per study of drug and lifestyle interventions. It is recognized that the ICERs of a study on lifestyle intervention in 1997 were the highest comparing to studies later on (10 to 16 of the logarithm of the ICERs)[5] .[19] The reason for this could be the high incremental costs with little gain of health effects (see Table 7 in appendix). The rest of the studies on lifestyle interventions showed more stable ICERs. However, from the results of one study in 2008, a great range within ICERs could be observed (between approximately 3 and 8 of the logarithm of ICERs).[18] An explanation could be the inclusion of discount rate in their study. When the cost and effects were undiscounted, lifestyle intervention dominated standard care for both men and women within a certain range of age; when the costs and effects were discounted, the ICERs tend to be higher irrespective of the gender (See 7 in appendix). Further, the ICERs of drug intervention remained quite stable by time. Between the two studies that have conducted economic evaluation on statin treatment in 2005, one showed higher ICERs (between 12 and 14 of the logarithm of the ICERs) and have concluded unfavourable ICERs compared to its current therapy.[24] This could be explained by the little gain in effects of this intervention for comparing to other studies. Further, the extent of scenarios analyses varied little. The minor difference was in the statin doses that were added as scenario in studies on drug intervention. However, a difference was found in the choice of scenarios between lifestyle and drug interventions. It was suspected that the outcomes of the included economic evaluations on lifestyle interventions were based on study perspectives,[8] gender, [18−19] discount rates,[18] CVD risks[19] and without specific scenarios,[17] The included economic evaluations on drug treatment had different scenarios on CVD risks and gender,[16,20,24] reimbursement schemes,[25]

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[5]Because of the great differences in the ICERs (see Tables 7,9,11,12 in appendix), a logarithm is implemented in order to be comparable.
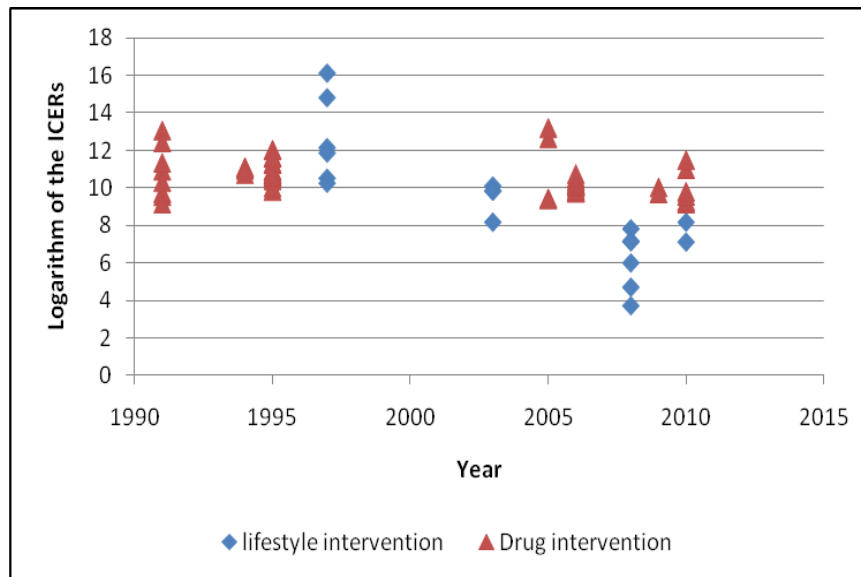
Figure 2: The change of ICERs by time

inclusion of exclusion of non-CVD costs,[20] time horizon[26] and without specific scenarios.[21−23] Studies on both interventions have included gender and CVD risks. However, the studies on lifestyle were more interested in scenarios such as different study perspectives or discount rates. Nevertheless, studies on drug interventions were interested in reimbursement schemes and costs. From these observations, one could suspect a potential relationship between the selection of scenarios and funding source.

When observing the robustness, the results of sensitivity analysis indicated that almost every study concluded that their outcomes were robust respective to the change of model parameters. Univariate sensitivity analysis testing at least one variable was mainly used on assessing the robustness of the outcomes. Five out of eight studies on statin treatment[16,20−23] and two out of four studies on physical activity and diet interventions[8,19] conducted a one or more way sensitivity analysis; the rest of the studies[17−18,25] conducted a probabilistic sensitivity analysis. Two studies on statin treatment have conducted both univariate and probabilistic sensitivity analysis.[24,26] It can be observed that studies on lifestyle interventions mainly have selected one parameter in their sensitivity analysis; no clear alignments were found within the studies on lifestyle interventions. For drug treatment, discrepancies were observed between the choices of parameters within the seven studies that have conducted one-way sensitivity analyses. In general, many studies have a diversity of parameters in their sensitivity analysis. A majority of studies on drug interventions has chosen for the change of discount rates and different CVD costs.[16,20−21,24,26] Besides that, lipid-lowering effects have been selected by some studies.[16,21,23] Further, no clear consistencies in the choice of parameters were found between studies on both types of interventions. However, it is observed that a minority of studies on lifestyle and drug interventions has

selected utility weights for their sensitivity analysis.[8,21,24,26] Finally, it was challenging to find the range of variables that were included in these sensitivity analyses, because many studies did not describe the range of uncertainty.

3.3 Key findings based on the BMJ quality checklist

The quality checklist of BMJ was used in this systematic review to assess the quality of economic evaluations on both lifestyle and drug interventions.[30] Tables 14 and 15 in appendix illustrate the percentage of fulfilment for the 35 questions for economic evaluations on both interventions. In general, from the 35 questions, 24 questions on lifestyle and 17 on statin treatment fulfilled above 70% in stating their research question, economic relevance of the study. In the section about data collection, the form of economic evaluation, the source of effectiveness, primary outcome, currency price, detail and justification of the choice of model were mostly adequately reported with a fulfilment percentage.

However, some justification problems were found on both types of interventions. In economic evaluations on both types of interventions, the rationale of choosing alternative programs was poorly reported. Only half of the studies on lifestyle and minority of drug interventions have stated the alternative program with additional explanation (50% of lifestyle[8,19] and 13% of statin treatment[26]). In the section of interpretation of results and analysis, it was recognized that a majority of lifestyle and statin studies (25% of lifestyle[17] and 50% of statin treatment[20−22,26]) did not or indistinctly mention the time horizon of their studies. Further, studies on both types of interventions mainly failed to justify their choice of discount rate; only a minority of studies have fulfilled this (0% of lifestyle and 22% of statin treatment[21,25−26]). This also holds for the choice of the variables, the percentages of fulfilment of studies on drug interventions are relatively lower comparing with lifestyle interventions. (50% of lifestyle[8,18−19] and 6% of statin[21]) and the range (63% of lifestyle[8,18−19] and 0% of statin) for their sensitivity analysis. As it is observed, in the field of sensitivity analysis, studies on drug interventions have scored more poorly than lifestyle intervention.

In addition to the justification issue, documentation problems are also observed. A great proportion of studies have not discussed the relevance of including or excluding costs of productivity loss (75% of lifestyle[8,17−18] and 100% of statin treatment[16,20−26]) Further, minor details on currency and inflation adjustments were given (both 25%[17,21−22]). Last, many studies did not mention the time horizon of their studies (75% of lifestyle[8,18−19] and 50% of statin treatment[16,23−25]).

No large differences in quality between studies on lifestyle and drug interventions were found. However, some minor differences can be mentioned. When focusing on the methodology of data collection, firstly, a slight difference was observed in the section of providing details on the design and results of effectiveness studies. In the economic evaluations on drug interventions, less than half of the studies did provide sufficient information about their effectiveness studies regardless whether their study was based on meta-analysis or a single study (40% on single studies[20,22,24−25], 17% on meta-analysis[21]). In the economic evaluations on lifestyle interventions, all studies have given sufficient information on their effectiveness study; these were all based on a single study. Further, more than half of the studies on drug interventions did not illustrate their quantities of resource separately from their unit costs; from all studies less than half have fulfilled this requirement (44%[16,20−22,26]). These studies mainly

presented direct medical costs but did not mention their unit costs and quantities used per patient group separately. On the contrary, all lifestyle studies fulfilled this criterion. Nevertheless, most studies have presented their outcomes in aggregated and disaggregated form (100% of lifestyle[8,17−19] and 88% of statin treatment[20−26]). Studies usually presented a summary index with the ICERs based on their comparisons (aggregated form). When reporting data in a disaggregated manner, this indicates that the outcomes of the studies are reported separately based on different scenarios. This is to allow readers to calculate other ratios of that he or she sees fit.[30] Last, all studies have answered their study question and conclusions based on the data that they have reported.

3.4 Potential relationships between factors and differences between lifestyle and drug interventions

After the characteristics, outcomes and quality elements are listed in detail, potential relationships between different types of study characteristics, study characteristics and outcomes are assessed within/across studies. Further, it is observed to what extent the associations differ between the two interventions.

3.4.1 Potential relationships between different types of study characteristics

When observing the study perspective, a great relationship is expected between the perspective of the study and the type of costs that have been taken into account. Nevertheless, some studies that were conducted from a societal perspective did not include indirect costs in their study. This occurred for studies both on lifestyle and drug interventions.

   The way in which future costs and benefits of interventions are discounted could have great influence on the economic evaluation of a given intervention.[31] The higher the discount rate, the lower the net present value of future costs and benefits. it is confirmed from viewing table 2,5, and 6 in appendix that studies had different approaches of discounting. The choice of discount rate had a pattern for Europe and was different from the patterns seen in North America, Australia and Asia. All cost-effectiveness studies that conducted in Europe had a discount rate of 3% annually. The studies conducted in North America and Australia opted for a discount rate of 5% annually.[16,19−20,23] Only one study on statin treatment conducted in the United States chose for a 3% discount rate.[26] Inconsistencies have been found in discount rates in Asia, A study conducted in Japan[24] chose for a 3% discount rate and Korea[21] chose for a 5% discount rate. Further, no clear differences were found between the choice of discount rate between the studies on the economic evaluation of lifestyle prevention and statin treatment.

3.4.2 Potential relationships between study characteristics and outcome

In this section, the potential relationships between study characteristics and outcomes are observed. In general, the observed relationships hold for both interventions. Thus, no systematic differences were found between lifestyle and drug interventions.

   From the included economic evaluations, a relationship is found between the type of population, risk factors and the study outcome. Within study, it seems that the higher the CVD risk, the more

favourable the ICER keeping the other variables constant.[16,19−20] This holds for both lifestyle and drug interventions. Furthermore, two studies on lifestyle intervention showed that when focusing on the economic evaluations that present gender-specific results within the same CVD risk range, the ICERs of men tend to be more favourable than that of women.[18−19] Consistent conclusions have been found in studies on drug intervention that have also chosen for CVD risks with gender selection of scenarios. Thus, it is concluded that for studies on both interventions, within in the same CVD risk range, the ICERs of men tends to always be more favourable than women.[16,18−20,24]

A relationship can be found between the time horizon and the ICERs. It seems that the ICERs are more favourable for studies with a limited time horizon than for studies with a lifetime time horizon. For example, it is observed in a study on statin treatment that the incremental costs of statin with a limited time horizon (median 3 years) tends to be much lower than in other studies with lifetime time horizons.[22] Consistent results are observed for a study on lifestyle interventions with a limited time horizon of three years.[17]

It is observed from studies on both types of interventions[19,21,26] that the ICER from cost-utility analysis tends to be lower than cost-effectiveness analysis. For example, an economic evaluation on lifestyle interventions[19] calculated that video and self-help intervention for men was €186,899 per LYG and €140,390 per QALY. Consistent results have showed in other studies.[21,26]

In a study on lifestyle intervention, it is recognized that when indirect costs were considered (societal perspective), the total costs have increased by costs of productivity losses.[8] When health effects remain the same, the ICER of societal perspective tends to be higher than health payer perspective. However, there is only one study within both interventions that have included indirect costs and calculated the results based on both a health payer and a societal perspective.[8] The rest of the studies did nor included or separated direct and indirect costs. Thus, there is not enough evidence to state an opinion on the relation between the inclusion of different types of costs and study outcome.

No systematic differences have been found in the relationship between funding source and the ICER. In general, statin therapy was regarded to be cost-effective in comparing with no treatment or placebo. One study has determined that statin therapy did not have a favourable ICER for their specific country and was highly dependent on the risk of CVD.[24] Unfortunately, the funding source of that study was not stated.[25] There is a possibility that there was no funding for that study. Further, none of the reviewed studies on statin treatment were funded by government or institute and likewise for lifestyle interventions. Previously, in section 3.2, it is observed that the two types of intervention had slightly different scenario settings. The studies on lifestyle interventions were more interested in the study perspective and discount rate and the studies on drug intervention favoured for scenarios such as CVD costs and reimbursement criteria. As it is mentioned earlier, one could assume that funding has potential association with the selection of scenarios. This could be observed by their choice of scenarios such as reimbursement schemes and including costs for studies on drug intervention. However, there is not enough evidence regarding these twelve studies that may lead to positive relationship between funding source and the ICERs.

4. Discussion

The objective of this systematic review was to gain more insight on the divergence of methodologies between economic evaluations on lifestyle interventions compared with drug interventions in the primary prevention of cardiovascular diseases. Further, this study was also interested in potential relationships between different factors (e.g. time horizon, funding source, incremental cost-effectiveness ratios and etc.) and to what extent these associations hold for these two interventions. In general, no great differences have been found between the methodology in conducting economic evaluation between lifestyle and drug interventions. Some minor variations in study characteristics were found, i.e. the choice of population, comparator, perspective, intervention time and time horizon. Nevertheless, it is noticed that transparency and documentation of the methodology was lacking in many studies on both types of interventions. A shortage in explanations of study approaches was observed in several factors such as stating the time horizon, intervention period, range and variables of sensitivity analysis, choice of comparator and discount rate.

When investigating the relationships between study characteristics within/across studies, some associations were observed. It is observed that the association between study perspective and the included costs was not clear. In studies on both interventions, it is found that societal perspective was not always adhered in terms of the costs included. In addition, a clear relationship was found between the discount rates and countries that the studies were conducted in. Furthermore, some associations have been discovered between study characteristics and outcome. It is observed that CVD risk factors, type of economic evaluation, time horizon and inclusion of additional costs interventions could have an influence on the ICERs. However, it was observed that there was not enough evidence to relate a positive relationship between funding and ICERs. Overall, the observed associations hold for both lifestyle and drug interventions.

In order to facilitate policy making and future researches on economic evaluations, transparency problems in documentation should be tackled. Further, potential differences between methodology on different types of interventions and relationships between factors and their influence on study results should be acknowledged. This way, comparability increases between studies. In the following section, possible explanations and further recommendations will be given on these results.

4.1 Discussion on the minor systematic differences

The report of Wanless has concluded that the standard principles of public health economic evaluations are the same as others such as clinical interventions.[32] However, it is true that the practical difficulties associated with methodology of economic evaluation of public health interventions are greater.[5-7] This systematic review has found consistent results as the statement of Wanless. Minor systematic differences have been found in the results of these twelve studies. These differences were also quite expectable because the difference of aims between clinical and lifestyle interventions and the context these studies were in. Thus, the general elements in the methodology between lifestyle and drug interventions seem to be consistent. However, a recent review on the methodology challenges of public health interventions concluded that studies on public health interventions particularly challenge in areas:

attribution outcomes to interventions to obtain unbiased estimates of effects (effects beyond RCTs); measuring and valuing outcomes (outcomes beyond the QALY); equity considerations, discounting, choice of type of sensitivity analysis and identifying intersectoral costs.[6] This systematic review has confirmed most of these challenges such as identifying intersectoral costs, obtaining effects beyond the outcomes of RCTs and methods dealing with uncertainty; these will be discussed through the discussion.

4.2 Discussion on the quality of studies

From the results of the selected studies and outcomes of the quality checklist by BMJ, many studies have shown a justification problem in various factors such as intervention time, time horizon, sensitivity analysis, choice of perspective and comparator. First, the approach, range and the choice of the variables for sensitivity analysis are mostly poorly written which could question the trustworthiness of the outcomes of these sensitivity analyses. A review recently performed in Sweden on economic evaluations on lifestyle interventions discusses that when cost-effectiveness studies are performed with lacking details as described earlier, it could be problematic to draw a trustworthy conclusion[11]. Consistent results were found in several other studies.[8−10,33−34] Moreover, the authors stated that the trade-off between accuracy and transparency is not always applicable[11]. Even on expectations that the studies would be transparent or accurate; it is still a challenge to guarantee that the studies are performed adequately. For example, it is often seen that economic evaluations in general report average cost-effectiveness ratios that may be difficult for policy makers to decompose overall results, or may not fully appreciate the importance of each element of data or assumption.[33] Another example is that it is observed in this systematic review that many studies do not adequately report the choice of variables and their range in sensitivity analysis. A study commented that authors often give an appearance of stability of their findings by omitting important parameters from consideration or by varying them by a small amount.[34] Thus, it is never safe to lay a direct relationship between accuracy and transparency because one study could be very accurate but fail or have no incentive to report their methodology truthfully. For this reason, more interests have been put in reporting guidelines for economic evaluations in order to increase transparency.[30,33−35]

It can be expected that the quality of economic evaluations would improve with increase of time and importance of economic evaluation. The reason for this could be more awareness in precision in study outcomes and quality of intervention that facilitates policy making.[36−38] A study pointed out that from the thirteen countries in Europe, economic evaluations on drug interventions are mainly used on reimbursement decisions (N=11) followed with communication to prescribers (N=7) and local formulary decisions (N=6).[37] This indicates that for policy making, economic evaluation is an important instrument to settle on an adequate policy in different settings. Further, it is resulted that cost-effectiveness studies before 2000 were slowly being switched to cost-utility analysis more recently. A possible explanation is the growth of attentiveness in comparison between study effects; it is shown that besides the effect on mortality, health-related quality of life has gained its importance.[27] Further, no clear trend was found in the field of quality improvement for more recently published economic evaluations. Regardless of the previous statement on accuracy and transparency, a lack of quality improvement still leads to a substantial issue that questions the consistency and transparency of the future economic evaluations. The interpretation and approach to measure these aspects should be aligned in studies in order to reduce

vulnerability and facilitate economic evaluations.

4.3 Discussion on potential relationships between factors

Firstly, studies on both types of interventions have inconsistent study perspectives in relation to the methodologies of conducting their economic evaluations. By this, it is meant that numerous studies with a societal study perspective did not include indirect costs and benefits such as productivity forgone in terms of monetary value into their calculations and unrelated healthcare costs. A lack of explanation has been found for not including these costs that led to confusions. One can expect that the difficulty exists to include unrelated healthcare costs because of the broad nature of public health interventions. It is mentioned in a research that studies on public health interventions often challenge in identifying intersectoral costs and consequences.[6] The previous study has commented that the impact of public health intervention is often wide-ranging. The costs and effects of lifestyle interventions could fall in many parts of the public sector, it challenges to identify all relevant costs and benefits affected by the intervention. An explanation for not including unrelated healthcare costs could be the unavailability of data and sometimes imprecise data.[27] This indicates that it is often challenging to gather patient specific data than taking an average of the total healthcare expenditure. Further, indirect costs such as informal care often lack valuation methods that are both theoretically valid and empirically feasible.[39] For example, it is challenged to measure the time of informal care and divide this into informal care and daily activities given by the caregiver. For economic evaluations in general, it is also recognized that many studies fail to include all relevant costs.[34] It is mentioned in a study on methodological flaws of economic evaluations that by adopting a broad societal viewpoint in general raises the biggest measurement challenges and may be tempting for studies to omit items for the benefit of the study.[34] In these situations, it is necessary to judge whether the omitted items would have a potential difference in study results. This would increase difficulties for health decision-makers to make efficient choices. The same study confirmed the importance the adherence to the chosen perspective. Thus, based on the results of this review, the reliability of the study perspective is questioned. This may be another indication for more attention when setting scientific guidelines for conducting an economic evaluation.

Second, it is recognized that there is a clear difference in the perspective of lifestyle and drug interventions. Conducting studies on drug treatment from a health-payer perspective could be seen as a logical conclusion, because these studies were funded by the pharmaceutical industry. Thus, these companies may not have enough incentive to include other costs outside of their interests. However, from a policy maker point of view, a societal study perspective for both costs and effects is still preferred in guidelines for several countries such as Australia, Canada, France, Spain, and the Netherlands.[3,37] By considering all relevant costs an optimal societal decision can be made. When not all costs are considered, it could lead to inefficient allocation of resources, on a short-term as well as on a long-term basis.[12,40] However, in the United Kingdom, it is advised in the guideline of technology appraisal that perspectives for costs and effects should be differed. The perspective of costs should have impact on costs and savings for the NHS (national health services) and personal social services; the perspective on outcomes should contain all health effects on individuals.[41] Nevertheless, in the reviewed study that have included United Kingdom in their study did not adhere to this advice when measuring health effects.[22]

Thus, it may be unattractive for studies on drug interventions to take a societal point of view for their interests in reimbursement issues and clinical effectiveness. Nevertheless, when other relevant costs such as productivity losses are left out, important differences could be neglected in both costs and effects of the prevention.

Third, a review on cost-effectiveness studies conducted in the Netherlands has shown that a difference in source funding may have substantial influences on the outcome of the study.[9] It is concluded that studies funded by pharmaceutical companies generally showed more favourable cost-effectiveness ratios because these companies have the intention to increase or attract more target group in the low CVD risk population group and generate more profit.[9,34] However, the results of our systematic review did not provide enough evidence on the statement of the review performed by Franco et al. 2005.[9] With a further glance, the conclusion from this review was based on comparing the ICERs of studies funded by pharmaceuticals and government or institutes. It results that there is a striking difference in ICERs between these two funding sources in low CVD risks. However, the government funded none of the studies on drug treatment in this systematic review. Thus, even a positive relation is shown between funding source and the ICERs, it is still inconclusive to confirm the statement from the previous study.

Fourth, approximately 50% of the studies on statins stated that placebo was their comparator. The rest of the studies compared their intervention with 'no intervention' or 'current therapy'. In general, placebo is often chosen as a comparator because it is the most commonly used comparator in clinical trials. From a policy point of view, placebo or no therapy are rarely good comparators in an economic evaluation where the comparator should be the most commonly used or the best alternative treatment besides the new treatment.[42] This indicates that when the best alternative is used as comparator, it assists the policymaker to decide on which intervention is most suitable to implement. However, manufacturer or sponsor may have the incentive to show its own therapy in a good light when their therapy is compared to placebo because of a more increase in treatment effects.[34] One study commented that the cost-effectiveness of a given therapy can only be judged in relation to one or more alternatives, which may include "doing nothing". The choice of alternative is critical because it provides the basis incremental cost-effectiveness analysis.[34] It can be expected that when using placebo or no therapy, the incremental effects would be higher than when using current therapy as comparator because placebo and no therapy have initially no treatment effect. Simultaneously, incremental costs would also increase. Nevertheless, the trade-off between incremental costs and effects are dubious which could lead to lower or higher ICER as result. From a decision maker point of view, results of the ICER take a great proportion in implementing a treatment. Thus, it would still not be beneficial for the pharmaceuticals when their treatment leads to a lower ICER than the current therapy. As conclusion, by comparing new drug intervention to current therapy as alternative would have potential benefits for both pharmaceuticals and policy makers.

Fifth, no distinct relationship is found between the uses of study design for both interventions. Studies on statins and on lifestyle have conducted their study based on RCT, modelling or both. It is being concerned that with the evaluation of medical technologies in most published guidelines, indicate a preference for evidence from RCTs comparing to relevant alternatives.[6] In the reviewed studies, we observed a greater proportion of modelling studies in studies on drug and lifestyle interventions. One

of the potential challenges of economic evaluations on public health interventions is the attribution of effects.[6] Since there are likely to be fewer controlled trials of public health programmes, other approaches such as modelling or quasi-experiments might be necessary for obtaining unbiased estimates of intervention effects. In this systematic review, it is recognized that many outcomes were often short-term. However, from a policy point of view, it is often favourable to view the costs and benefits in the long term in order to decide on which intervention to implement.[6] However, it is important to keep in mind it might be quite logical that RCTs do not cover costs and effects for a longer period; many modelling studies extrapolate the results of RCTs to extend the time horizon of the intervention. Besides the difference in time horizon of RCT and modelling studies, RCT effect data may also chooses a narrower inclusion criteria what could favours the outcome. Further, RCTs are often criticized that they are unable to accommodate the complexity and flexibility that characterises public health programmes than drug interventions. This is also one of the challenges of conducting economic evaluations on public health interventions.[6] RCTs are often judged as relatively simple and unvarying interventions. Thus, in several studies, it is confirmed that RCTs are often inappropriate for public health settings.[6,43−44] The outcomes of RCTs determine the causal relationship between the intervention and outcomes. However, study design alone cannot suffice as main criterion for credibility of evidence about public health interventions.[44]

Sixth, one of the potential challenges of public health interventions is the method of estimating uncertainty of the study. In this systematic review, it is observed that minor studies have conducted probabilistic sensitivity analysis and this holds for both lifestyle and drug interventions. From the results from these twelve studies, it is observed that irrespective of the choice of sensitivity analysis, almost all studies have concluded that the outcome of the sensitivity analysis indicated robust with respect to model parameters. There have been debates on which methods is the most suitable for economic evaluations and some researchers recommended that probabilistic sensitivity analysis should be required in all cases and others think simpler methods will suffice.[45] It is mentioned that when a probabilistic analysis is conducted properly, it provides an approach by requiring that all input parameters in a model be specified as full probability distribution, rather than as point estimates, to indicate the uncertainty of the estimates.[46−48] Other approaches such as univariate sensitivity analysis are often recognized as too simple because it only tests one variable at a time by holding others constant; when variables are correlated, it becomes more complicated to determine the relationship and effect of the parameter on the outcome. Within these twelve studies, some have conducted one-way sensitivity with more variables. However, a probabilistic sensitivity analysis is recommend in order to receive a more complete picture of the parameter uncertainty in the model and lead to higher additional value of information.[49]

Last, it is resulted from the reviewed studies that the choice of discount rate mainly differed for Europe (3%) compared to North America (5%), Australia (5%) and Asia (3-5%). This choice is consistent with the different guidelines for specific countries.[36] For example, a review on potential differences in health technology assessment (HTA) guidelines pointed out that in Australia and Canada, it is formalized to choose a discount rate of 5% in order to meet the reimbursement criteria.[36] However, the review mentioned that several informal guidelines exists which are only voluntarily followed by studies such as countries like United States and Ireland.[36] Studies in these countries are advised to set a discount rate, but no specific range is given in these guidelines. Furthermore, HTA guidelines in Asia have emerged

in the last few years; it is expected that the implementation of HTA guidelines will catch up with the progress in Western countries.[50] This may explain the inconsistencies in discount rate from the studies in Asia. However, the conclusions of this review were only based on medical economic evaluations. For studies on lifestyle interventions, there is not enough evidence to have similar conclusions because studies on public health interventions are not as well established as compared to drug interventions.[1,6] A report on economic evaluation in the social welfare field showed that studies on public health interventions have started increasing after 1996.[1] However, this is still a minority compared to medical economic evaluations. More researches are continuing on the field of public health interventions.[7]

4.4 Limitations

This systematic review faces several limitations. First, a narrowed PICO model is used in this systematic review; this could limit potential additional findings. For example, lifestyle interventions were only focused on the combination therapy of diet and physical activity in this study. This led to only four studies for review, which could be too little for an adequate quality assessment and comparisons between studies on lifestyle and drug interventions. The outcomes of the methodology assessment could be different when other types of lifestyle interventions were chosen.

Second, there are minor doubts about the objectivity of the BMJ quality checklist. From 35 questions, it is assumed that all questions have an equal weight. Nevertheless, one can expect that some questions such as giving the details of currency information may weigh less than others such as methodological sections. Peer reviewing the selected articles may reduce subjectivity. However, there were inconsistencies in answers because of widely questions and ended answers such as yes and no answers. Thus, through consensus meetings with both peer-reviewers, an agreement is formed on these items. However, it is inconclusive to state a strong opinion on the absolute quality of these studies.

Last, this review has only focused on studies on preventive interventions on both lifestyle and drug interventions. It is resulted that minor systematic differences exists between these two interventions. However, from a broader perspective, the conventional economic evaluations have more focused on clinical interventions. Guidelines that have been established and are discussed in this review are also mainly based on drug conventional economic evaluations. It is concluded from this systematic review that the potential methodological issues exist among preventive interventions. However, it is not sure whether the results of this review holds for economic evaluation as a whole (e.g. medical treatments) ; this is beyond the scope of this research.

5. Conclusion and recommendations

In this systematic review, minor systematic differences have been found in the methodology on economic evaluations between lifestyle and drug interventions. Similar conclusion could be made for the observation on potential relationships between different factors (between study characteristics, study characteristics and outcomes within/across studies). Nonetheless, it is resulted from this systematic review that transparency problem in documentation exists within these twelve studies. These problems exist mainly in several factors such as stating the time horizon, intervention period, range of variables of sensitivity

analysis, choice of comparator and discount rate. The transparency issues that have been recognized between these characteristics may be caused by the lack of adequate guidelines in conducting an economic evaluation. This could hinder health policy making on mainly reimbursement and implementation decisions. In order to reduce these challenges, two recommendations are suggested. First, for developing countries, governmental sectors should put more attention in conducting sufficient guidelines for economic evaluations that researches could follow. Further, it is suggested for policymakers to increase formalization in established guidelines; this would obligate the researchers to follow the recommendations by monitoring research activities. Both recommendations will reduce transparency problems as well as methodology inconsistencies that would increase overall quality of economic evaluations in the long term. In addition, this review recommends that more attention should be put in conducting quality checklists. It cannot be denied that subjectivity remains in assessing the quality of studies. However, it was often difficult to judge the article per question because some of them were quite unclear and could lead to multiple answers. One can suggest rephrasing some questions in order to receive more definite and reliable answers. For future research, more investigations should be made in the field of methodology on economic evaluations in general, quality of guidelines and checklists. This would enhance comparability between interventions and assist policymaking in various settings.

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6. Appendix

Search terms for Medline, Scopus and NHS-HTA-EED

Medline

Cost-effectiveness studies ("Costs and Cost Analysis"[mh] OR "Cost-Benefit Analysis"[mh] OR cost benefit*[ti] OR cost effect*[ti] OR cost utility[ti] OR cost efficien*[ti] OR econom*[ti] OR pharmacoeconomic*[ti] OR pharmaco-economic*[ti] OR (cost*[ti] AND (effect*[ti] OR benefit*[ti] OR quality[ti] OR efficien*[ti])) OR (cost*[ti] AND economics[majr]))

Prevention (prevention[tiab] OR preventive[tiab] OR screening[tiab] OR health promotion[tiab] OR health protection[tiab] OR intervention*[tiab] OR health protection[tiab] OR health promotion[mh] OR healthy people programs[mh] OR preventive health services[mh] OR health surveys[mh] OR mass screening[mh] OR primary prevention[mh] OR public health[tiab] OR accident prevention[mh] OR preventive medicine[mh])

Cardiovascular disease (cardiovascular diseases[mh] OR cardiovascular[ti] OR angina[ti] OR stroke[ti] OR blood pressure[ti] OR myocardial[ti] OR ischaemic[ti] OR ischemic[ti] OR coronary[ti] OR heart[ti] OR atherosclerosis[ti] OR cerebrovascular[ti] OR cardiac[ti]) Physical activity programs: (life style[tiab] OR lifestyle[tiab] OR life style[mh] OR physical activity[tiab] OR physical inactivity[tiab] OR motor activity[mh:noexp] OR exercise*[tiab] OR exercise[mh] OR locomotion[tiab] OR sedentary behavior[tiab] OR sedentary behaviour[tiab] OR physical fitness[tiab] OR physical therapy[tiab] OR physical training[tiab] OR physical education[tiab] OR fitness[tiab] OR aerobics[tiab] OR sports[tiab] OR sports[mh] OR counsel*[tiab] OR self-management[tiab] OR health education[tiab])

Diet programs (overweight[tiab] OR obesity[tiab] OR obesity[mh] OR dietetics[tiab] OR diet[tiab] OR diets[tiab] OR dieting[tiab] OR diet therapy[mh] OR nutrition therapy[tiab] OR weight loss[tiab] OR weight loss[mh] OR body weight changes[mh] OR weight gain[mh] OR fruit[tiab] OR vegetables[tiab] OR sodium chloride[tiab] OR fish oils[tiab] OR calories[tiab] OR dietary fats[tiab] OR dietary fats[mh] OR diet, fat-restricted[mh] OR diet, carbohydrate-restricted[mh] OR diet, sodium restricted[mh] OR diet, reducing[mh] OR fasting[mh] OR fasting[tiab] Or healthy eating[tiab] OR high fat*[tiab] OR low fat*[tiab] OR fatty food*[tiab])

Statin (Hydroxymethylglutaryl-CoA Reductase Inhibitors[Mh] OR statins[tiab] OR statin therapy[tiab] OR statin drug[tiab] OR statin drugs[tiab] OR statin use[tiab] OR "coa reductase inhibitors"[tiab])

Scopus

Cost Effectiveness studies TITLE((cost-benefit*) OR (cost-effect*) OR (cost-utility) OR (cost-efficien*) OR econom* OR pharmacoeconomic* OR (pharmaco-economic*)) OR KEY((cost-benefit*) OR (cost-effect*) OR (cost-utility) OR (cost-efficien*) OR (costs-and-cost-analysis)) OR (TITLE(cost*) AND TITLE(effect* OR benefit* OR quality OR efficien*))

Prevention   TITLE-ABS-KEY((prevention) OR (preventive) OR (screening) OR (health-promotion) OR (health-protection) OR (intervention) OR (public-health) OR (health-promotion) OR (healthy-people-programs) OR (preventive-health-services) OR (health-surveys) OR (mass-screening) OR (primary-prevention) OR (accident-prevention) OR (preventive-medicine))

Cardiovascular disease   TITLE(cardiovascular OR angina OR stroke OR (blood-pressure) OR myocardial OR ischaemic OR ischemic OR coronary OR heart OR atherosclerosis OR cerebrovascular OR cardiac)

Physical activity programs   TITLE-ABS-KEY((life-style) OR (physical-activity) OR (physical-inactivity) OR (motor-activity) OR (exercise) OR (locomotion) OR (sedentary-behavior) OR (sedentary-behaviour) OR (physical-fitness) OR (physical-therapy) OR (physical-training) OR (physical-education) OR (fitness) OR (aerobics) OR (sports) OR (counseling) OR (self-management) OR (health-education)

Diet programs   TITLE-ABS-KEY((overweight) OR (obesity) OR (dietetics) OR (diet) OR (diets) OR (dieting) OR (nutrition-therapy) OR (weight-loss) OR (fruit) OR (vegetables) OR (sodium-chloride) OR (fish-oils) OR (calories) OR (dietary-fats) OR (fasting) OR (healthy-eating) OR (high-fat) OR (low-fat) OR (fatty-food) OR (obesity) OR (diet-therapy) OR (weight-loss) OR (body-weight-changes) OR (weight-gain) OR (dietary-fats) OR (diet-fat-restricted) OR (diet-carbohydrate-restricted) OR (diet-sodium-restricted) OR (fasting))

Statin   TITLE-ABS-KEY ((CoA-Reductase-Inhibitors) OR statins OR (statin-therapy) OR (statin-drug) OR (statin-drugs) OR (statin-use))

NHS-EED-HTA

Cost-effectiveness studies   (“Costs and Cost Analysis” OR “Cost-Benefit Analysis” OR cost benefit* OR cost effect* OR cost utility OR cost efficien* OR econom* OR pharmacoeconomic* OR pharmaco-economic* OR (cost* AND (effect* OR benefit* OR quality OR efficien*)) OR (cost* AND economics))

Prevention   (prevention OR preventive OR screening OR health promotion OR “health protection” OR intervention* OR “health protection” OR “health promotion” OR “healthy people programs” OR “preventive health services” OR “health surveys” OR “mass screening” OR “primary prevention” OR “public health” OR “accident prevention” OR “preventive medicine”)

Cardiovascular diseases   (“cardiovascular diseases” OR cardiovascular OR angina OR stroke OR “blood pressure” OR myocardial OR ischaemic OR ischemic OR coronary OR heart OR atherosclerosis OR cerebrovascular OR cardiac)

Physical activity programs   ("life style" OR lifestyle OR "physical activity" OR "motor activity" OR exercise* OR exercise OR locomotion OR "sedentary behavior" OR "sedentary behaviour" OR "physical fitness" OR "physical therapy" OR "physical training" OR "physical education" OR fitness OR aerobics OR sports OR sports OR counsel* OR "self management" OR "health education")

Diet programs   (overweight OR obesity OR obesity OR dietetics OR diet OR diets OR dieting OR "diet therapy" OR "nutrition therapy" OR "weight loss" OR "weight loss" OR "body weight changes" OR "weight gain" OR fruit OR vegetables OR "sodium chloride" OR "fish oils" OR calories OR "dietary fats" OR "dietary fats" OR "diet, fat-restricted" OR "diet, carbohydrate-restricted" OR "diet, sodium restricted" OR "diet, reducing" OR fasting Or "healthy eating" OR high fat* OR low fat* OR fatty food*)

Statins   ("Hydroxymethylglutaryl-CoA Reductase Inhibitors" OR statins OR statin therapy OR statin drug OR statin drugs OR statin use OR coa reductase inhibitors)

Table 1: Study characteristics of lifestyle interventions (physical activity and diet)

Author(s), year	Population, Risk factor	Intervention	Comparator	Study design	Short-term effectiveness measures	Long-term effectiveness measures
Salkeld et al '97[19]	Individuals between 18 and 69 years old, no chronic illness and with one or more CVD risk factors.	Physical activity and diet	Standard care	RCT and (Markov) model	Blood pressure, BMI, smoking status and cholesterol level.	QALY/ LYG
Lindgren et al '03[8]	60-year-old cohort with no prior CVD history, diabetes or other severe diseases; no regular use of drugs.	Diet, physical activity or both counselling	No intervention	(Markov) model	Reduction of DBP, cholesterol level.	LYG
Galani et al '08[18]	Individuals between 25 and 85 years old with overweight.	Physical activity and diet	Standard care	(Markov) model of a hypothetical cohort	BMI, systolic pressure, cholesterol level, high-density lipoprotein cholesterol.	QALY
Eriksson et al '10[17]	Individuals between 18 to 65 years old with Moderate to high risk to CVD.	Supervised physical activity training and diet counselling (with standard care)	Standard care	RCT	Quality of life	QALY

Abbreviations: RCT: randomized controlled trials, QALY: quality adjusted life years, LYG: life years gained, TTO method: time trade method, BMI: body mass index, DBP: diastolic blood pressure.

Table 2: Study characteristics of lifestyle interventions (physical activity and diet) (Continued)

Author(s), year	Type of costs	Discount rate: costs and effects	Price year	Perspective	Funding	Intervention period	Time horizon	Country
Salkeld et al '97[19]	Direct costs: hospitalization, rehabilitation, follow-up and procedures, follow-up care, drug therapy, nursing home, hostel care. Indirect costs: production losses of people before and after CVD events.	5% annually	1994 Australian dollars	Health payer/ Societal perspective	Government	1 year*	8 years*	Australia
Lindgren et al '03[8]	Direct costs: direct health expenditures. Indirect costs: loss of production and costs in added years of life. (Difference between production and consumption due to extra survival)	3% annually	SEK adjusted to 2000 years CPI.	Health payer/ Societal perspective	Government	2 years*	Lifetime*	Sweden
Galani et al '08[18]	Direct costs: dietician costs, physical activity costs.	3% annually	Swiss France CHF adjusted to 2006 CPI.	Societal perspective	Government	3 years	60 years*	Switzerland
Eriksson et al '10[17]	Direct costs: program costs for stakeholders, participant's expenses and health care costs.	3% annually	Price level of 2009 using Swedish CPI.	Societal perspective	Government	3 years	3 years	Sweden

Abbreviations: CPI: consumer price index.

*: Not directly stated

Table 3: Study characteristics of drug intervention (statin treatment)

Author(s), year	Population Risk factor	Intervention	Comparator	Study design	Short-term effectiveness measures	Long-term effectiveness measures
Hay et al '91[16]	Individuals between 35 to 55 years old with no CVD history	Lovastatin	Placebo*	Not stated	Total cholesterol levels	LYS
Martens et al '94[23]	A cohort of 45-years old men with no CVD*.	Fluvastatin, Lovastatin, Pravastatin and Simvastatin	No treatment/ Fluvastatin	Mathematical model of CVD morbidity, mortality and treatment costs (reduction of CVD risks for each year)	Cholesterol level, LDL, HDL	LYS
Hamilton et al '95[20]	Individuals between 30 and 70 years had no previous CVD history but elevated cholesterol level.	Lovastatin	Placebo*	CVD prevention model (annual probability of dying from CVD or other causes of CVD events.	Cholesterol level, HDL-C	LE
Nagata-Kobayashi et al '05[24]	Individuals between 45 to 70 years old for men and 55 to 70 years old for women with hypercholesterolemia and no history of CVD.	Pravastatin	No treatment	(Markov) model	Total cholesterol levels	QALY

Abbreviations: HDL: high-density lipoprotein, LDL: low-density lipoprotein, HDL-C: high-density lipoprotein cholesterol, LYS: life year saved, LE: life expectancy, QALY: quality adjusted life years.

*: Not directly stated

Table 4: Study characteristics of drug intervention (statin treatment) (continued)

Author(s), year	Population, Risk factor	Intervention	Comparator	Study design	Short-term effectiveness measures	Long-term effectiveness measures
Lindgren et al '05[22]	Individuals between 40 and 79 years old with untreated or treated hypertension but no CVD but at least three other risk factors.	Atorvastatin	Placebo	RCT	Total number of CVD events and procedures avoided	Idem
Nash et al '06[25]	Individuals above 40 years old who are free of CVD and have 10-year fatal cardiovascular risk of at least 5% based on the European guidelines of CVD prevention.	Atorvastatin, Rosuvastatin, Fluvastatin, Simvastatin (generic), Simvastatin, Pravastatin (generic), Pravastatin	No treatment	(Markov) model	Probability of death and AMI according to age, risk of AMI, age-specific cardiac mortality rates, relative risk of death.	QALY
Kang et al '09[21]	Individuals above 45 years old with no CVD history.	Atorvastatin, Simvastatin	No treatment	(Markov) model	Total cholesterol levels	QALY, LYG
Ohsfeldt et al '10[26]	Individuals at a Framingham risk score of ¿10% risk of CVD with no history of CVD.	Rosuvastatin	Placebo	RCT and (Markov) model	Relative risk of an event with Rosuvastatin treatment	QALY, LYS

Abbreviations: QALY: quality adjusted life years, LYG: life years gained, LYS: life years saved, AMI: acute myocardial infarction.

Table 5: Study characteristics of drug intervention (statin treatment) (continued)

Author(s), year	Type of costs	Discount rate: costs and effects	Price year	Perspective	Funding	Intervention period	Time horizon	Country
Hay et al '91[16]	Direct costs	5% annually. (Effects*, costs: not stated)	1989 U.S dollars	Individual patient perspective	Pharmaceutical	Life time (Up to age 75)	Lifetime (Up to age 75)*	US
Martens et al '94[23]	Direct costs: physician visits, treatment costs and laboratory tests (drug costs, monitoring costs).	5% annually.	1993 Canadian CPI	Not Stated	Pharmaceutical	Lifetime	Lifetime*	Canada
Hamilton et al '95[20]	Direct costs: drug costs, physician visits, Laboratory tests: blood test samples, lipid profiles, biochemical profiles and treatment costs.	5% annually.	Adjusted to 1992 CPI.	Societal perspective	Pharmaceutical	Lifetime	Lifetime*	Canada
Nagata-Kobayashi et al '05[24]	Direct costs: treatment and hospitalization costs	3% annually	Adjusted to Yen 2002 CPI.	Societal perspective	Not stated	Lifetime	Lifetime*	Japan
Lindgren et al '05[22]	Direct costs: hospitalization, outpatient visits and drug costs.	No discounting	Adjusted to 2002 levels using CPI.	Health payer perspective	Pharmaceutical	Median: 3 years	Median: 3 years	Seven countries (Denmark, Iceland, Finland, Norway, Ireland, Sweden and UK)*

Abbreviations: CPI: consumer price index.

*: Not directly stated

Table 6: Study characteristics of drug intervention (statin treatment) (continued)

Author(s), year	Type of costs	Discount rate: costs and effects	Price year	Perspective	Funding	Intervention period	Time horizon	Country
Nash et al '06[25]	Direct costs: general practitioner review: lipid profiles and liver function tests.	3.5% annually	Adjusted to price year 2005	Health payer perspective	Not stated	Lifetime (Up to age 65)	Idem*	Ireland
Kang et al '09[21]	Direct costs: drug cost.	5% annually	Adjusted to price year 2008	Health payer perspective	Pharmaceutical	Lifetime	Idem*	Korea
Ohsfeldt et al '10[26]	Direct costs: annual physician visits, monitoring costs, event related treatment and hospitalization costs.	3% annually	Adjusted to price year 2008	Health payer perspective	Pharmaceutical	Life time (Up to age 100) or 10- and 20-years*	Idem*	US

*: Not directly stated

Table 7: Study outcomes of lifestyle interventions (physical activity and diet)

Author(s), year	Incremental costs	Incremental effects	ICERs
Salkeld et al '97[19]	1) Video group: €166 pp. 2) Video self-help group: men: €275 for men; women: €297.	1) Video and Self-help LYG: men: 0,001492, women: 0,000102. 2) QALY: men: 0,001880 and women: 0,000028. 3) Video for high risk men: LYG is 0,002713 and QALY is 0,003618	1) Video and self-help: men: €186,899 per LYG. Women: €2,7million per LYG. 2) Video and self-help: men: €140,390 per QALY. Women: €10 million per QALY. 3) High risk group video: men: €36,397 per LYS and €27,929 per QALY.
Lindgren et al '03[8]	1) Declining effect: Societal perspective: €385 and payer perspective: €296. 2) Remaining effect: societal perspective: €1159 and payers perspective: €220**	1) Declining effect: Societal and payerÕs perspective: 0,016 LYG. 2) Remaining effect, societal and payers perspective: 0,063 LYG**	1) Declining effect: Societal: ICER €24,045 and healthcare perspective: €18,492/LYG. 2) Remaining effect: Societal: €18,384 and health payer perspective: €3487/LYG.**
Galani et al '08[18]	1) Undiscounted: lifestyle intervention dominates standard care for female between 40 to 60 years and male between 30 to 60 years. 2) Discounted: female: €284 ¡IC¡ €392. Male: €224 ¡IC¡ €242.	1) Undiscounted: 0,41 ¡QALY¡ 0,91 2) Discounted: 0,16 ¡QALY¡ 0,37	1) Undiscounted: female: Dominant ¡ICER¡ €1266/QALY. 2) Undiscounted: male: Dominant ¡ICER¡ €395/QALY. 3) Discounted: female: €108 ¡ICER¡ €2435/QALY. 4) Discounted: male: €40 ¡ICER¡ €1223/QALY. All results depend on age and overweight/obesity.
Eriksson et al '10[17]	€242 pp.	1) Using EQ-5D gained QALY: 0.08. 2) Using EQ-VAS: 0.20 and SF-6D: 0.07. All outcomes depends on Qol scales.	€1202 ¡ICER¡ €3468/QALY

Abbreviations: QALY: quality adjusted life years, EQ-5D: European quality of life-5 dimensions, SF-6D: Short form 6D 6-dimensions, EQ-VAS: European quality of life visual analog scale, Qol: Quality of life.

**: Calculated

Table 8: Study outcomes of lifestyle interventions (physical activity and diet) (continued)

Author(s), year	Article's conclusion	Sensitivity analysis	Results sensitivity analysis
Salkeld et al '97[19]	Lifestyle interventions targeted at high-risk males could be more cost-effective than people with standard risk. Indirect benefits do not have significant effect on the overall results.	Univariate: maintenance of behaviour change through time and indirect costs.	If changes in risk factors persist for 2 years (instead of base case 1 year): ICER is €60812 per QALY for men and €7,8 million per QALY for women. The cost-effectiveness of lifestyle intervention improves significantly if behavioural changes are maintained over time.
Lindgren et al '03[8]	Based on the prediction of the model, diet intervention appears to be the most cost-effective among 60 years old men in the county of Stockholm.	Univariate: QALY	When using QALY in a sensitivity analysis, the results are equally good.
Galani et al '08[18]	Lifestyle intervention can be regarded as cost-effective only in certain situations depending on sex, age, and threshold value.	Probabilistic	Lifestyle intervention had a higher probability of being cost-effective in moderate obese male subjects comparing to overweight subjects from the same age group. Within the moderate obese group, lifestyle intervention had a higher probability to be cost-effective in male subjects comparing to female subjects from the same age group.
Eriksson et al '10[17]	Lifestyle intervention in primary care improves QOL and is highly cost-effective in relation to standard care.	Probabilistic	Using the threshold of €4800 as willingness to pay for a QALY, the probability of cost-effectiveness is 0,985 using SF- 6D, 0,886 using EQ-5D and 0.999 using EQ-VAS.

Abbreviations: QALY: quality adjusted life years, EQ-5D: European quality of life-5 dimensions, SF-6D: Short form 6D, 6-dimensions, EQ-VAS: European quality of life visual analog scale, Qol: Quality of life.

Table 9: Study outcomes of drug intervention (statin treatment)

Author(s), year	Incremental costs	Incremental effects	ICERs
Hay et al '91[16]	*	*	1) Average risk men: €14,300 ¡ICER¡ €16,800/LYS. 2) Average risk women: €55,600 ¡ICER¡ €471,880/LYS. 3) High risk (smoking and hypertension) men: €9533 ¡ICER¡ €84,200/LYS. 4) High risk women: €30,187 ¡ICER¡ €252,413/LYS. All outcomes depend on age and smoking status.
Martens et al '94[23]	For a 45 year old person who smoke: 1) Fluvastatin: €8086 2) Pravastatin: €12,432 3) Lovastatin: €12,115 4) Simvastatin: €12,410 **	For a 45 year old person who smoke (LYS): 1) Fluvastatin: 0,174 2) Pravastatin: 0,185 3) Lovastatin: 0,191 4) Simvastatin: 0,215	1) Fluvastatin: €46,416/LYS 2) Pravastatin: €67,232/LYS 3) Lovastatin: €63,404/LYS 4) Simvastatin: €57,781/LYS
Hamilton et al '95[20]	1) Low risk men: €13,039 ¡IC¡ €44,482. 2) Low risk women: €16,500 ¡IC¡ €50,100 3) High risk men: €8700 ¡IC¡ €37,350 4) High risk women: €12,125 ¡IC¡ €43,650	1) Low risk men: 0,23 ¡IE¡ 1,44 2) Low risk women: 0,42 ¡IE¡ 0,99 3) High risk men: 0,23 ¡IE¡ 2,04 4) High risk women: 0,37 ¡IE¡ 1,10	1) Low risk men without non-CVD costs: €38,574 ¡ICER¡ €79,395/LYG. 2) Low risk women without non-CVD costs: €48,345 ¡ICER¡ €164,000/LYG. 3) Low risk men with non-CVD costs: €43,905 ¡ICER¡ €83,000/LYG. 4) Low risk women with non-CVD costs: €55,694 ¡ICER¡ €169,200/LYG. 5) High risk men without non-CVD costs: €18,709 ¡ICER¡ €46,100/LYG. 6) High risk women without non-CVD cost: €33,160 ¡ICER¡ €110,608/LYG. 7) High risk men with non-CVD cost: €22,673 ¡ICER¡ €54,376/LYG. 8) High risk women with non-CVD cost: €39,769 ¡ICER¡ €114,778/LYG.

Abbreviations: IC: incremental costs, IE: incremental effects, ICER: incremental cost effectiveness ratio, QALY: quality adjusted life years, LYG: life years gained, LYS: life years saved.

*: Not directly stated, **: Calculated

Table 10: Study outcomes of drug intervention (statin treatment) (continued)

Author(s), year	Article's conclusion	Sensitivity analysis	Results sensitivity analysis
Hay et al '91[16]	Cholesterol medication could be economically justified, partially for persons with high level of primary CVD risk factors.	Univariate: cholesterol reduction, daily therapy costs, discount rate, years to achieve benefits, medical costs, index of survival after initial heart disease event, therapy compliance, bed disability (Percentage of healthy days)	Base case results are quite stable. Large changes in key parameters have a little effect on model results.
Martens et al '94[23]	It is more cost-effective to initiate treatment with Fluvastatin than with Pravastatin, Lovastatin or Simvastatin.	Univariate: lipid lowering effect of Fluvastatin	The results were stable to a 23% variation in the percentage of LDL reduction from original assumption.
Hamilton et al '95[20]	The cost-effectiveness of HMG-CoA reductase inhibitors (statin) varied widely by age and sex and was also sensitive to the presence of non-lipid CVD risk factors. When the HDL-C effect is considered, HMG-CoA reductase inhibitor is quite cost-effectiveness comparing to other lipid therapies.	Univariate: cost of the drug, discount rate.	The cost-effectiveness results are sensitive to the change in cost in medication and discount rate.
Nagata-Kobayashi et al '05[24]	The cost-effectiveness of Pravastatin therapy for primary prevention varies widely depending on the combination of cardiac risks. The QALY of preventive Pravastatin therapy did not compare favorably with that of currently accepted therapeutic or diagnostic interventions implemented in Japan.	1) Univariate: Incidence of MI, proportion of patients with MI under invasive treatment, case fatality rate of MI, recurrence rate of MI, RR of MI, medical costs, utility and discount rate. 2) Probabilistic: transitional probabilities, costs and utilities.	Sensitivity analysis for baseline cases, no variables had a meaningful effect on ICER. ICER did not exceed under €70,000 per QALY with any combination of variables. For probability sensitivity analysis, it is indicated that 90.7% of trials showed that Pravastatin is more costly at ¿€35,600/QALY.

Abbreviations: QALY: quality adjusted life years, HDL-C: high density lipoprotein-cholesterol, MI: myocardial infarction, LDL: low density lipoprotein, RR: relative risk, ICER: incremental cost effectiveness ratio.

Table 11: Study outcomes of drug intervention (statin treatment) (continued)

Author(s), year	Incremental costs	Incremental effects	ICERs
Nagata-Kobayashi et al '05[24]	Persons aged 60: 1) Men: €15,811 2) Women: €19,023	Persons aged 60: 1) Men: 0,05 2) Women: 0,035	Low cardiac risk group (Total cholesterol level of 240mg/dl): 1) Men: ICER: €313,375/QALY 2) Women: ICER: €541,285/QALY For high cardiac risk groups = ICER highly dependent on the risk.
Lindgren et al '05[22]	1) Sweden: €450 2) UK: €424**	0,035 events avoided for all events and procedures.	1) Sweden: €12,700/Per event avoided. 2) UK: €12,000/Per event avoided.
Nash et al '06[25]	Not stated	Not stated	GMS reimbursement scheme: 1) Atorvastatin: €17,155/QALY 2) Rosuvastatin: €17,730/QALY 3) Fluvastatin: €17,922/QALY 4) Simvastatin (generic): €20,040/QALY 5) Simvastatin: €26,164/QALY 6) Pravastatin (generic): €25,639/QALY 7) Pravastatin: €32,394/QALY DP reimbursement scheme: 1) Atorvastatin: €23,480/QALY 2) Rosuvastatin: €24,439/QALY 3) Fluvastatin: €25,000/QALY 4) Simvastatin (generic): €28,750/QALY 5) Simvastatin: €37,090/QALY 6) Pravastatin (generic): €37,376/QALY 7) Pravastatin: €46,482/QALY

Abbreviations: QALY: quality adjusted life years, GMS scheme: general medical services scheme, DP scheme: drug payment scheme, ICER: incremental cost effectiveness ratio.

**: Calculated

Table 12: Study outcomes of drug intervention (statin treatment) (continued)

Author(s), year	Incremental costs	Incremental effects	ICERs
Kang et al '09[21]	€1,5 million	1) 92,72 QALY gained	1) €22,792/LYG
		2) 67, 93 LYG gained	2) €16,697/QALY
Ohsfeldt et al '10[26]	1) Lifetime: €319million	1) Lifetime: 29,817 LYG, 335,000 QALY gained.	1) Lifetime: €9573/QALY, €10,748/LYG
	2) 20 years: €370million	2) 20 years: 20,438 LYG, 254,000 QALY gained.	2) 20 years: €14,563/QALY, €18,083/LYG
	3) 10 years: €600million	3) 10 years: 6069 LYG, 99,000 QALY gained.	3) 10 years: €60,278/QALY, €98,494/LYG

Abbreviations: QALY: quality adjusted life years, LYG: life years gained, ICER: incremental cost effectiveness ratio.

Table 13: Study outcomes of drug intervention (statin treatment) (continued)

Author(s), year	Article's conclusion	Sensitivity analysis	Results sensitivity analysis
Lindgren et al '05[22]	For a population without previous CVD, 10 mg dose per day of Atorvastatin appears to be a cost-effective treatment strategy.	Univariate: Variation in assumptions about the fraction of patients undergoing PCI or CABG.	Variation in assumptions about the fraction of patients undergoing PCI or CABG had only a small impact on the results.
Nash et al '06[25]	A majority of statins is cost-effective in primary prevention of patients with high risk of developing CVD under GMS scheme. Atorvastatin is the 10mg cost- effective whilst pravastatin 40mg falls outside of the threshold for cost-effectiveness. (€46,482/QALY)	Probabilistic: for the most cost-effective Statin (10mg Atorvastatin)	There is 80% chance of being cost-effective whilst treating a high-risk primary prevention GMS population with 10mg, using a threshold of €46,482/QALY.
Kang et al '09[21]	Statin therapy was very likely to be cost-effective in the prevention of CVD for Korean aged older than 45 years.	Univariate: cholesterol lowering effects, CVD risk predictions, CVD costs and utility weights and discount rate.	None of the changes in the model inputs altered the conclusions in the base case. Probability of being cost-effective was greater at a threshold of €33, 000/QALY (93, 7%) €22,000/QALY (53, 8%).
Ohsfeldt et al '10[26]	Rosuvastatin treatment of 20mg daily was cost-effective in reducing Cardiovascular morbidity and mortality comparing to no treatment. This intervention is cost- effective in patients with higher CVD risks. (Framingham risk ¿ 10%). Lifetime ICER per QALY was well below the WTP of $50,000/QALY.	1) Univariate: discontinuation, subsequent prevention statin initiation, event costs, event disutilityÕs, discounting, event risk and event relative risk. 2) Probabilistic: event costs, event disutilityÕs and relative risk of event.	Both univariate and probabilistic analysis indicated robust with respect to most model parameters.

Abbreviations: QALY: quality adjusted life years, GMS scheme: general medical services scheme, ICER: incremental cost effectiveness ratio, PCI: percutaneous coronary intervention, CABG: coronary bypass graft surgery, WTP: willingness to pay.

Table 14: BMJ quality checklist of lifestyle intervention (physical activity and diet)

Checklist items[30]	Percentage of fulfilment	Salkeld et al '97	Lindgren et al '03	Galani et al '08	Eriksson et al '10
Study design					
1. The research question is stated.	100%	✓	✓	✓	✓
2. The economic importance of the research question is stated.	100%	✓	✓	✓	✓
3. The viewpoint(s) of the analysis are clearly stated and justified.	75%	✓	✓	/	/
4. The rationale for choosing alternative programmes or interventions compared is stated.	50%	✓	✓	✗	✗
5. The alternatives being compared are clearly described.	88%	✓	/	✓	✓
Data collection					
6. The form of economic evaluation used is stated.	100%	✓	✓	✓	✓
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	75%	✓	✓	✗	✓
8. The source(s) of effectiveness estimates used are stated.	100%	✓	✓	✓	✓
9. Details of the design and results of effectiveness study are given (if based on a single study).	100%	✓	✓	N/A	✓
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	0%	N/A	N/A	✗	N/A
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	100%	✓	✓	✓	✓
12. Methods to value benefits are stated.	75%	✓	✓	✗	✓
13. Details of the subjects from whom valuations were obtained were given.	88%	/	✓	✗	✓
14. Productivity changes (if included) are reported separately.	50%	✓	✓	✓	✓
15. The relevance of productivity changes to the study question is discussed.	25%	✓	✗	✗	✗
16. Quantities of resource use are reported separately from their unit costs.	100%	✓	✓	✓	✓
17. Methods for the estimation of quantities and unit costs are described.	88%	✓	✓	✓	✓
18. Currency and price data are recorded.	100%	✓	✓	✓	✓
19. Details of currency of price adjustments for inflation or currency conversion are given.	25%	✗	✗	✗	✓

Checklist items[30]	Percentage of fulfilment	Salkeld et al '97	Lindgren et al '03	Galani et al' 08	Eriksson et al '10
20. Details of any model used are given.	100%	✓	✓	✓	N/A
21. The choice of model used and the key parameters on which it is based are justified.	100%	✓	✓	✓	N/A
Analysis and interpretation of results					
22. Time horizon of costs and benefits is stated	25%	✗	✗	✗	✓
23. The discount rate(s) is stated.	100%	✓	✓	✓	✓
24. The choice of discount rate(s) is justified.	0%	✗	✗	✗	✗
25. An explanation is given if costs and benefits are not discounted.	0%	N/A	N/A	✗	N/A
26. Details of statistical tests and confidence intervals are given for stochastic data.	83%	✓	N/A	/	✓
27. The approach to sensitivity analysis is given.	100%	✓	✓	✓	✓
28. The choice of variables for sensitivity analysis is justified.	50%	/	/	✓	✗
29. The ranges over which the variables are varied are justified.	63%	✓	/	✓	✗
30. Relevant alternatives are compared.	50%	✓	✓	✗	✗
31. Incremental analysis is reported.	100%	✓	✓	✓	✓
32. Major outcomes are presented in a disaggregated as well as aggregated form.	100%	✓	✓	✓	✓
33. The answer to the study question is given.	100%	✓	✓	✓	✓
34. Conclusions follow from the data reported.	100%	✓	✓	✓	✓
35. Conclusions are accompanied by the appropriate caveats.	75%	✓	✓	✓	✗

✓: item adequately addressed, ✗: item inadequately addressed, N/A: not applicable, /: item partial addressed, r: referred to reference.

Table 15: BMJ quality checklist of drug intervention (statin treatment)

Checklist items[30]	Percentage of fulfillment	Hay et al '91	Martens et al '94	Hamilton et al '95	Nagata-Kobayashi et al '05	Lindgren et al '05	Nash et al '06	Kang et al '09	Ohsfeldt et al '10
Study design									
1. The research question is stated.	100%	✓	✓	✓	✓	✓	✓	✓	✓
2. The economic importance of the research question is stated.	75%	✓	✗	✓	✓	✓	✓	✓	✗
3. The viewpoint(s) of the analysis are clearly stated and justified.	50%	/	✗	/	/	✓	✗	/	✓
4. The rationale for choosing alternative programmes or interventions compared is stated.	13%	✗	✗	/	✗	/	✗	✗	✓
5. The alternatives being compared are clearly described.	60%	✗	✗	/	✗	✓	✓	✓	✓
Data collection									
6. The form of economic evaluation used is stated.	100%	✓	✓	✓	✓	✓	✓	✓	✓
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	50%	✓	✗	✓	✗	✓	✗	✗	✓
8. The source(s) of effectiveness estimates used are stated.	88%	✓	✗	✓	✓	✓	✓	✓	✓
9. Details of the design and results of effectiveness study are given (if based on a single study).	40%	✗	N/A	/	✗	✓	/	N/A	✓
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	17%	N/A	✗	N/A	N/A	N/A	✗	/	N/A
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	100%	✓	✓	✓	✓	✓	✓	✓	✓
12. Methods to value benefits are stated.	82%	✓	✓	✓	✓	✓	✓	✓	✓
13. Details of the subjects from whom valuations were obtained were given.	69%	/	✗	✓	✓	/	✗	✓	✓
14. Productivity changes (if included) are reported separately.	0%	N/A	N/A	✗	✗	N/A	N/A	N/A	N/A
15. The relevance of productivity changes to the study question is discussed.	0%	N/A	N/A	✗	✗	N/A	N/A	N/A	N/A
16. Quantities of resource use are reported separately from their unit costs.	44%	/	✗	/	✗	✓	✗	/	/
17. Methods for the estimation of quantities and unit costs are described.	75%	✓	✓	✓	✗	✓	✗	✓	✓

Checklist items[30]	Percentage of fulfilment	Hay et al '91	Martens et al '94	Hamilton et al '95	Nagata-Kobayashi et al '05	Lindgren et al '05	Nash et al '06	Kang et al '09	Ohsfeldt et al '10
18. Currency and price data are recorded.	100%	✓	✓	✓	✓	✓	✓	✓	✓
19. Details of currency of price adjustments for inflation or currency conversion are given.	25%	✗	✗	✗	✗	✓	✗	✓	✗
20. Details of any model used are given.	100%	✓	✓	✓	✓	N/A	✓	✓	✓
21. The choice of model used and the key parameters on which it is based are justified.	72%	✓	✗	✓	✓	N/A	✗	✓	✓
Analysis and interpretation of results									
22. Time horizon of costs and benefits is stated	50%	✗	✗	✓	✗	✓	✗	✓	✓
23. The discount rate(s) is stated.	93%	/	✓	✓	✓	N/A	✓	✓	✓
24. The choice of discount rate(s) is justified.	22%	✗	✗	✗	✗	N/A	✓	/	✗
25. An explanation is given if costs and benefits are not discounted.	100%	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A
26. Details of statistical tests and confidence intervals are given for stochastic data.	14%	✗	✗	N/A	✗	/	✗	/	✗
27. The approach to sensitivity analysis is given.	50%	✗	✗	✗	✓	✗	✓	✓	✓
28. The choice of variables for sensitivity analysis is justified.	6%	✗	✗	✗	✗	✗	✗	/	✗
29. The ranges over which the variables are varied are justified.	0%	✗	✗	✗	✗	✗	✗	✗	✗
30. Relevant alternatives are compared.	6%	✗	✓	/	✗	✗	✗	✗	✗
31. Incremental analysis is reported.	75%	✗	✓	✓	✓	✓	✗	✓	✓
32. Major outcomes are presented in a disaggregated as well as aggregated form.	88%	✓	✓	✓	✓	✓	✓	✓	✓
33. The answer to the study question is given.	100%	✓	✓	✓	✓	✓	✓	✓	✓
34. Conclusions follow from the data reported.	100%	✓	✓	✓	✓	✓	✓	✓	✓
35. Conclusions are accompanied by the appropriate caveats.	63%	✓	✓	✗	✓	✓	✗	✓	✗

✓: item adequately addressed, ✗: item inadequately addressed, N/A: not applicable, /: item partial addressed, r: referred to reference.