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Protective effect on mortality of active commuting to work:

A systematic review and meta-analysis

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Running title: Active commuting and mortality

Abstract

Background: Sedentary behaviour is a major risk of mortality. However, data are contradictory regarding the effects of active commuting on mortality.

Objectives: To perform a systematic review and meta-analysis on the effects of active commuting on mortality.

Method: The PubMed, Cochrane Library, Embase, and Science Direct databases were searched for studies reporting mortality data and active commuting (walking or cycling) to or from work. We computed meta-analysis stratified on type of mortality, type of commuting, and level of commuting, each with two models (based on fully adjusted estimates of risks, and on crude or less adjusted estimates).

Results: 17 studies representing 829 098 workers were included. Using the fully adjusted estimates of risks, active commuting decreased all-cause mortality by 9% (95% confidence intervals 3 to 9%), and cardiovascular mortality by 15% (3 to 27%) ($p < 0.001$). For stratification by type of commuting, walking decreased significantly all-cause mortality by 13% (1 to 25%), and cycling decreased significantly both all-cause mortality by 21% (11 to 31%) and cardiovascular mortality by 33% (10 to 55%) ($p < 0.001$). For stratification by level of active commuting, only high level decreased all-cause mortality by 11% (3 to 19%) and both intermediate and high level decreased cardiovascular mortality. Low level did not decrease any type of mortality. Cancer mortality did not decrease with walking nor cycling, and the level of active commuting had no effect. Low level walking did not decrease any type of mortality, intermediate level of walking decreased only all-cause mortality by 15% (2 to 28%), and high level of walking decreased both all-cause and cardiovascular mortality by 19% (8 to 30%) and by 31% (9 to 52%), respectively. Both low, intermediate and high intensities of cycling decreased all-cause mortality. Meta-analysis based on crude or less fully adjusted estimates retrieved similar results, with also significant reductions of cancer mortality with cycling (23%, 5 to 42%), high level of active commuting (14%, 4 to 24%), and high level of active commuting by walking (16%, 0 to 32%).

Conclusion: Active commuting decreases mainly all-cause and cardiovascular mortality, with a dose-response relationship, especially for walking. Preventive strategies should focus on the benefits of active commuting.

Key Points

Physical inactivity is one of the leading causes of death in developed countries increasing notably all-cause, cardiovascular and cancer mortality. There were contradictory findings regarding the effect of sedentary transport to or from work on mortality.

We demonstrated that active commuting decreases both all-cause and cardiovascular mortality, whatever the type of active commuting to or from work, with a dose response relationship.

Preventive strategies should focus on the benefits of active commuting to or from work in the general population.

1 Introduction

Sedentary lifestyle is a major public health problem ¹⁻³. Physical inactivity is one of the leading causes of death in developed countries ⁴ increasing notably all-cause, cardiovascular and cancer mortality ^{5,6}. In particular, sedentary transport modes have been described as a factor increasing mortality ⁷⁻¹², despite conflicting results ^{13,14} and relatively few studies focusing solely on workplace displacement ¹⁴⁻¹⁶. Nearly half of the population is working worldwide, i.e. more than 3 billion workers ¹⁷. For available data in some developed countries, less than 10% of workers go to work using active commuting like walking or cycling ¹⁴, whereas 50% of workers live within 8 km of their workplace ^{18,19}. Demonstrating benefits of active commuting on mortality can be of major importance to promote effective preventive strategies based on changing behavior when going to work ²⁰⁻²³. Moreover, the benefits of leisure-time physical activity on mortality has been largely demonstrated ^{2,13,24}, without clear comparisons between walking and cycling. There is also a clear dose-response relationship between level of leisure-time physical activity and mortality reduction ²⁵⁻²⁹. These relationships remain to be determined for active commuting to or from work, particularly in light of limitations observed in a previous meta-analyses (see section 4.2) ¹⁵.

Therefore, we aimed to conduct a systematic review and meta-analysis on the effect of active commuting to or from work on mortality, stratified by type of mortality (all-cause, cardiovascular, cancer), type of active commuting (walking or cycling) and level (low, moderate and high). Moreover, articles quantifying risks report very frequently different models of calculation of the same risk (depending on the method of calculation or adjustment models such as crude or adjusted hazard ratio). Thus, we used two models for each meta-analysis: a model using the most adjusted risks listed in included articles, and a model using only crude or less adjusted risks.

2 Methods

2.1 Literature search

We reviewed all studies reporting a risk of mortality depending on the type of commuting to go to work. The PubMed, Cochrane Library, Science Direct and Embase databases were searched on April 30th 2020, using the following keywords: “commuting” or “commute” and “mortality” (details of search strategy is presented in Electronic Supplementary Material Appendix S1). The search was not limited to specific years and no language restrictions were applied. To be included, articles needed to describe our primary outcome variables i.e. mortality data in relation with active commuting. In addition, reference lists from all publications meeting the inclusion criteria, and from reviews retrieved with our keywords, were manually searched to identify any further studies that were not found using the electronic search. The search strategy is presented in Fig 1. Two authors (SP and FD) independently conducted all literature searches, collated and reviewed the abstracts and based on the selection criteria, decided the suitability of the articles for inclusion. A third author (BP) was asked to review the articles where consensus on suitability was debated. All authors then reviewed the eligible articles. We followed the guidelines outlined by PRISMA (Electronic Supplementary Material Appendix S2).

2.2 Data collection

The data collected included first author's name, publication year, study design, aims, outcomes of included articles, sample size, number of deaths, mean age, percentage of males, sex, type of mortality (all-cause, cardiovascular, cancer), type of active commuting (walking or cycling), level (low, moderate, high), risks data, type of risk (depending on method of calculation or adjustment model such as crude or adjusted odd ratio), methods of evaluation of active commuting within included studies (such as self-reported questionnaires or interviews),

methods of evaluation of mortality within included studies (such as details on death registry), and putative adjustment / explaining factors (such as geographical zone, body mass index (BMI), smoking, or leisure physical activity).

2.3 Quality of assessment

The Newcastle-Ottawa Scale (NOS) was used to check the quality of included articles³⁰. Two authors (SP and VN) evaluated the methodological quality of each included study using 8 items with a maximum score of 9 stars as points. The following 8 items were assessed in all cohort studies: 4 items on selection bias (representativeness of the exposed and non-exposed cohort, ascertainment of expose), 1 item divided in 2 sub-items on comparability bias (design and analysis) and 3 items on outcome bias (assessment of outcome, length and adequacy of follow-up). Similar items were used to evaluate case control studies. Each item was assigned a judgment of “Yes”, “No”, “Unclear”, or “Not applicable”. One point was given for each item within the selection and exposure categories, and a maximum of two points was given for the comparability item involving the control of the most important factor and any specific control for others important factors. Disagreements were addressed by obtaining a consensus with a third author (FD).

2.4 Statistical considerations

Statistical analysis was conducted using Stata software (v15, StataCorp, College Station, US). Baseline characteristics were summarized for each study sample and reported as means \pm standard deviations and number (%) for continuous and categorical variables respectively. Heterogeneity of the study results was evaluated by examining forest plots, confidence intervals (CI) and using formal tests for homogeneity based on the I-squared (I^2) statistic. I^2 is easily

interpretable and the most common metric to measure the magnitude of between-study heterogeneity. I^2 values range between 0% and 100% and are typically considered low for <25%, modest for 25–50%, and high for >50%³¹. For example, a significant heterogeneity may be due to the variability between the characteristics of the studies such as those of workers (age, sex, etc), type of mortality, type of commuting, or level of commuting. Random effects meta-analyses (DerSimonian and Laird approach) were conducted when data could be pooled³². P values less than 0.05 were considered statistically significant.

We conducted meta-analysis on the effects of active commuting to or from work on mortality. We stratified these meta-analyses on the type of mortality (all-cause, cardiovascular, and cancer), the type of active commuting (cycling, and walking), and the level of active commuting (low, intermediate, and high). Moreover, we pay a particular attention to avoid the inclusion of the same cohort several times in the same analysis, to avoid that one cohort weights more than other cohorts. Therefore, for each meta-analysis, we computed two models (a model using the most adjusted risks listed in included articles, and a model using only crude or less adjusted risks). Similarly, for articles reported both hazard ratio for walking and hazard ratio for cycling, using the same control group of non-active commuters, we arbitrary chose to present data for cycling only, and to compute sensitivity analyses with walking only, in order to verify the absence of difference for stratification by type of mortality and by level of active commuting. Hazard Ratios were centered at one if the mortality of workers with active commuting did not differ from the mortality of workers without active commuting. Hazard Ratio >1 denoted an increased risk of mortality, and Hazard Ratio <1 reflected a decreased risk of mortality with active commuting to or from work. For rigor, funnel plots of these meta-analyses were used to search for potential publication bias. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect and Egger's test was used to assess publication bias³³. A value of $p < 0.05$ was considered statistically significant. In case of a significant

publication bias, Duval and Tweedie's trim and fill method was used to allow for the estimation of an adjusted effect size ³⁴. In order to verify the strength of the results, further meta-analyses were then conducted excluding studies that were not evenly distributed around the base of the funnel ³⁵. Similarly, when some workers may overlap between two studies, we also performed sensitivity analyses using only one cohort. Where possible (sufficient sample size), meta-regressions were proposed to study the relationship between active commuting and mortality and clinically relevant parameters such as the workers age (continuous data), and sex, the type of mortality, the type, and level of active commuting to or from work (categorical data). Results were expressed as regression coefficients and 95%CI.

3 Results

An initial search produced 96,124 articles (Fig 1). Removal of duplicates and use of the selection criteria reduced the number of articles reporting mortality and data to 17 articles^{7-14,16,22,36-42}. All articles were written in English. All studies reported that ethical approval had been obtained.

3.1 Quality of articles

The assessment of the quality of the 17 included studies was performed using the Newcastle Ottawa quality scale, varying from 55.6 ³⁸ to 100% ¹¹, with a mean score of 75.2±10.1. There was a low risk of bias for all data except for the assessment of exposure and outcomes (mostly self-reported) (Fig 2). To further elucidate risk of bias, we provide details in section 3.2 relating to the representativeness of the population for all studies except three that included only patients with type 2 diabetes ³⁶, hypertensive individuals ³⁷, or elderly workers ¹², together with study characteristics.

3.2 Population

Description of the sociodemographic of the workers included in our meta-analyses were lacking for several of the included articles because these data were part of a larger body of data on physical activity and active commuting in general, and most often only the sociodemographic of the entire cohort were described.

Sample size: Population sizes ranged from 2 538¹³ to 263 450¹⁴. In total, at least 829 098 workers were included in this meta-analysis. Only one study did not provide a detailed number of workers ¹¹. The prospective cohorts were representative of the general population, with or without diseases, except one study on workers with type 2 diabetes ³⁶, one on workers with hypertension ³⁷, and one on elderly workers ¹².

Sex: Similarly, sex was described sometimes only in workers, sometimes only for the general population, and sometimes for none of the study participants. Within the ten studies reporting sex of workers ^{7,8,13,14,16,37,40}, a total of 342 891 men were included compared to 339 350 women workers. Two studies described sex only for the general population ^{11,13} and five studies ^{9,12,36,38,39} did not specify the proportion of men or women both in workers or in the general population. All studies included both men and women except one study which included only women ¹¹ and one only men ¹⁶.

Age: All studies gave information on age: eleven studies for workers ^{9,10,12,14,16,22,36,37,40-42}, and six only for the general population ^{7,8,11,13,38,39}. Mean age ranged from 41 ⁴⁰ to 74 years ¹², and from 43 ⁸ to 62 years ³⁹, respectively. Among those studies, age by sex was reported in two studies for workers ^{37,40}, and in three studies for the general population ^{8,11,13}.

BMI: Similarly, fourteen studies reported BMI: nine studies reported BMI for the working population ^{10,12,14,16,22,36,37,40,42} – ranging from 21.9 ¹⁶ to 29.6 kg/m² ³⁶, and five studies reported BMI only for the general population ^{7,8,11,13,38} – ranging from 24.0 ¹¹ to 28.0 kg/m² ³⁸. Three studies did not report BMI ^{9,39,41}.

Smoking status: Thirteen studies reported smoking status: nine among workers^{10,12,14,16,22,36,40-42} – with a percentage ranging from 9%¹⁰ to 41%¹⁶, and four for the general population^{7,8,11,13} – ranging from 2%¹¹ to 68%⁷. Four studies did not report smoking status^{9,37-39}.

3.3 Aims and outcomes of included articles

In our meta-analyses, we included only mortality data in relationship with active commuting (walking, cycling) to or from work. However, the aim of the majority of the included studies was to examine the relationship between mortality and domain-specific physical activity (i.e. leisure time physical activity^{7-9,12,13,36,37,40}, activity at work^{7,9,13,40}, occupational physical activity^{8,12,36,37,39}, exercise or sports^{7,9-11,40}, active commuting in general^{10-13,22,38,39}; data on mortality and transportation to and from work were also reported^{7-14,16,36-40}. Only three studies focused on the mode of commuting to or from work^{14,16,41}. One study aimed to examine the individual, combined and isolated effects of movement-based behavior³⁸, and one study aimed to determine whether bicycle commuting was associated with a risk of injury⁴².

3.4 Study designs

All the 17 studies included had a prospective cohort design, describing hazard ratios for all-cause, cardiovascular and cancer mortality depending on the level of active commuting used. Seven studies were single-site^{7,9,10,12,16,39,40} and ten were multi-site^{8,11,13,14,22,36-38,41,42}. The majority of studies were conducted in Europe^{7-10,13,14,16,22,36,37,39-42}, followed by one in United-Sates³⁸, one in Japan¹² and one in China¹¹. The mean follow up ranged from 5³⁸ to 25 years¹⁶. Eight studies had a follow up <10 years^{10-12,14,22,38,41,42}, and nine studies had a follow-up greater than 10 years^{7-9,13,16,36,37,39,40}.

3.5 Evaluation of Active commuting within included studies

Active commuting was reported for both walking and cycling in thirteen studies ^{8-11,13,14,16,22,36-38,40,42} (among which 4 studies reported separately walking and cycling ^{10,11,14,42}), only cycling in three studies ^{7,39,41}, and only walking in one study ¹². All studies collected the type of commuting using self-reported questionnaires, except for one study that used interviews ¹¹. The questionnaires used in the studies were validated from the MONICA study (Monitoring of Trends and Determinants of Cardiovascular Disease) ⁴³ in seven studies ^{7-9,13,36,37,40}; the EPIC Physical Activity Questionnaire (EPAQ2) ⁴⁴ in two studies ^{10,39}; the Saltin and Grimby questionnaire ⁴⁵ in one study ⁹; the international physical activity questionnaire short form ⁴⁶ in one study ¹⁴, and a questionnaire specifically designed for other studies ^{12,16,22,38,41,42}. The level of active commuting was described in most studies by groups of intensity ^{13,22}, groups of duration in min/day ^{8,9,16,36,37} or in min/week ^{10,39}, groups of both intensity and duration (MET-hour/week) ^{11,41,42}, or groups of frequency in days/week ¹².

3.6 Evaluation of Type of mortality within included studies

The majority of the studies described the three types of mortality ^{9,11-14,16,22,39,40}. Three studies described only all-cause and cardiovascular mortality ^{8,10,36}, one described only data for cardiovascular mortality ³⁷, and two studies described only data for all-cause mortality. ^{41,42}.

3.7 Evaluation of Mortality within included studies

All studies retrieved mortality from the death registry obtained from health authorities, mostly from nationwide databases: the nationwide death register of Finland ⁸, National Health Service Central Registry of the UK ¹⁶, National Patient Registry of Denmark ^{9,41}, UK Office for National Statistics (ONS) ^{10,39}, National Health Service (NHS) of England, Wales and Scotland ^{14,22,42}, statistics Finland ^{36,37}, Social Security Administration and Medicare / Medicaid of USA ³⁸, National Vital Statistics Database from the Ministry of Health, Labour and Welfare of Japan ¹²,

Swiss National Cohort (SNC)⁴⁰. Local health authorities databases were used in one study¹³, and the unprecise – “vital statistics and cancer registry” – in one study¹¹. All the databases used the International Classification of Diseases (ICD) for reporting causes of mortality: the 8th revision¹⁶, the 9th revision^{11,13}, the 10e revision^{12,14,22,42}, the 8 and 9th revision⁹, the 9th and 10th revision³⁹, or the 8, 9, and 10th revisions^{8,36,37,40}. Even if not mentioned within the articles, the three other studies also used the ICD for type of mortality - data from UK Office for National Statistics (ONS), data from health services of the USA, and data from The National Patient Register and National Diabetes Registry of Denmark^{10,38,41}. One study did not give how mortality and cause of mortality was retrieved⁷.

3.8 Meta-analysis on the effect of active commuting on mortality

Meta-analysis stratified by type of mortality: Taking into account only the most adjusted hazard ratio data per study, active commuting decreased significantly both all-cause (HR=0.91, 95% CI 0.85 to 0.97) and cardiovascular (0.85, 95% CI 0.73 to 0.97) mortality, without significant effects for cancer mortality (0.92, 95% CI 0.81 to 1.03) (Fig 3 and Fig 4).

Meta-analysis stratified by type of commuting: Using the same methodology, active commuting by walking decreased significantly all-cause mortality by 13% (HR = 0.87, 95% CI 0.75 to 0.99), and active commuting by cycling decreased both all-cause mortality by 21% (0.79, 95% CI 0.69 to 0.89) and cardiovascular mortality by 33% (0.67, 95% CI 0.45 to 0.90), (Fig 3, and Electronic Supplementary Material Figs S1-S3). Active commuting by walking decreased non significantly cardiovascular and cancer mortality, and active commuting by cycling decreased non significantly cancer mortality.

Meta-analysis stratified by level of active commuting: Only high level decreased significantly all-cause mortality by 11% (HR = 0.89, 95% CI 0.81 to 0.97) and both intermediate and high level decreased cardiovascular mortality by 18 and 11% (0.82, 95% CI

0.66 to 0.98; and 0.89, 95% CI 0.78 to 1.00; respectively). Low level did not decrease any type of mortality (Fig 3 and Fig 5, and Electronic Supplementary Material Figs S4-S6).

Meta-analysis stratified by level of walking: Low level walking did not decrease any type of mortality, intermediate level of walking decreased only all-cause mortality by 15% (HR = 0.85, 95% CI 0.72 to 0.98), and high level of walking decreased both all-cause and cardiovascular mortality by 19% (0.81, 95% CI 0.70 to 0.92) and by 31% (0.69, 95% CI 0.48 to 0.91), respectively (Fig 3, and Electronic Supplementary Material Figs S7-S9).

Meta-analysis stratified by level of cycling: Both low, intermediate, and high intensities of cycling decreased all-cause mortality (0.86, 95% CI 0.75 to 0.97; 0.72, 95% CI 0.60 to 0.84; and 0.84, 95% CI 0.74 to 0.95; respectively) (Fig 3, and Electronic Supplementary Material Fig S10-S12). Despite some significant results on the effects of active commuting using cycling, the number of studies included precluded robust conclusions for cardiovascular and cancer mortality.

3.9 Publication bias and sensitivity analyses

Funnel plots (metafunnels) of meta-analyses (section 3.8) used for analysing potential publication bias are presented in Electronic Supplementary Material Fig S13. Meta-analyses reperformed after the exclusion of studies that were not evenly distributed around the base of the funnel showed similar results (data not shown). Egger's test was non-significant. To further address sensitivity analyses, we also reperformed aforementioned meta-analyses using crude or less adjusted hazard ratio (meta-analysis stratified by type of mortality: Electronic Supplementary Material Figs S14 and S15; meta-analysis stratified by type of commuting: Electronic Supplementary Material Fig S14, and S16-S18; meta-analysis stratified by level of active commuting: Electronic Supplementary Material Fig S14, and S19-S21; meta-analysis stratified by level of walking: Electronic Supplementary Material Fig S14, and S22-S24; meta-

analysis stratified by level of cycling: Electronic Supplementary Material Fig S14, and S25-S27; metafunnels of meta-analyses on crude or less adjusted hazard ratio: Electronic Supplementary Material Fig S28). In addition to all previous significant results using fully adjusted measures of risks, meta-analysis based on crude or less fully adjusted estimates retrieved similar results, with also a significant reduction of cancer mortality with cycling (HR = 0.77, 95% CI 0.56 to 0.95), high level of active commuting (0.86, 0.76 to 0.96), and high level of active commuting by walking (0.84, 0.68 to 1.00). Furthermore, sensitivity analyses using only walking data for studies reporting both hazard ratio for walking and hazard ratio for cycling, using the same control group of non-active commuters, showed similar results (data not shown). Lastly, excluding alternatively one of the two studies ^{14,42} that may have some degree of overlapping between their population showed similar results (data not shown).

3.10 Metaregressions

There were no effects of age or sex on the reduction of mortality from active commuting. Metaregressions also failed to demonstrate best outcomes depending on type of mortality (all-cause, cardiovascular, or cancer mortality) or level of active commuting (low, intermediate, high) – although we report greater effect sizes for high levels of walking compared to low or intermediate levels. Lack of data precluded further meta-regressions such as comparisons depending on geographical zone (country), body mass index, smoking, or leisure physical activity.

4 Discussion

The main findings were that active commuting to or from work decrease mainly all-cause and cardiovascular mortality, with a dose-response relationship, especially for walking.

4.1 The benefits of active commuting on mortality

Sedentary lifestyle is a major public health problem ³. Sedentary behavior in general increases the risk of sleep disturbance ⁴⁷ and poor mental health ⁴⁸, cardiovascular and metabolic diseases ^{5,6,49}, incidence of colon, breast, and endometrial cancer ⁵⁰, and mortality (all-cause, cardiovascular, cancer) ^{3,6,51,52}. To promote health benefits, national and international campaigns encourage a decrease in overall sedentary behavior by incorporating more physical activity in daily life, especially during commuting ⁴. In 1995, the CDC and the American College of Sports Medicine recommended a moderate amount of physical activity (e.g. 30 minutes of brisk walking) preferably every day ⁵³. Despite existing data regarding causes of mortality due to sedentary behavior ⁶, the putative effects of active commuting to and from work on mortality have been poorly studied ¹⁴⁻¹⁶. We demonstrated strong benefits on mortality of active commuting. Considering that most workers used their car for short distance to go to work ^{18,19}, active commuting could provide a significant change with strong public health benefits ^{20,23}. Furthermore, commuting by walking or cycling has a negligible cost compared to driving or public transport. Moreover, active commuting could partly reduce the most problematic global warming issue. Considering a mean petrol consumption of 5 liters per 100 km by car, there are 120 to 130 g of CO₂ emitted in the atmosphere per kilometer ⁵⁴. Taking into account the number of workers using a car for less than 5 km, commuting to and from work this practice can produce billions of tons of CO₂ emitted per year ⁵⁵. Therefore, in addition to health benefits, active commuting should also be promoted as an ecological target ^{56,57}.

4.2 All-cause and cardiovascular mortality are decreased by active commuting

The positive effect of leisure time physical activity on all-cause, cardiovascular and cancer mortality was largely demonstrated ^{1,24,40}, with conflicting results for active commuting to and from work. We demonstrated that active commuting to or from work decreased mainly all-cause and cardiovascular mortality whatever model was used, and with significant benefits for cancer mortality with crude or less adjusted meta-analyses. Our results do not agree with the previous meta-analysis which reported that active commuting only decreased all-cause mortality but not cardiovascular and cancer mortality ¹⁵. A possible explanation for this may relate to that our search strategy was more rigorous i.e. we included from 22 to 45% more articles (16, 11 and 7 articles instead of 11, 9 and 5 for all-cause mortality, cardiovascular and cancer mortality, respectively). Moreover, our meta-analysis was more rigorous by computing two models: one based on fully adjusted hazard ratio, and one based on crude or less adjusted hazard ratio. All models gave significant findings for all-cause and cardiovascular mortality. Finally, we also detailed a dose response-relationship considering the level of physical activity during active commuting.

4.3 Level of active commuting: a dose response relationship?

A large body of evidence suggests an independent dose-response between the level of leisure time, physical activity and mortality ^{9,58,59}. We also demonstrated that the highest intensities of active commuting in general had the strongest benefits, with also a dose-response relationship for active commuting by walking. Low, intermediate and high active commuting had a reduction of 4, 5, and 11% respectively for all-cause mortality. Interestingly, for cardiovascular mortality, we showed that even a low level tended to decrease mortality, in line with the literature showing that small amounts of physical activity (minutes) can also reduce mortality

⁶⁰. Consequently, going to work actively, even at a low level of activity during short periods, may have strong health benefits. Secondly, it can be noted that the decrease in cardiovascular mortality seemed to follow a U-shape, with stronger benefits for intermediate intensities. Although physical activity at work is confounded by socioeconomic status, this could be consistent with the literature showing that physical activity at work can be detrimental to life expectancy ^{61,62}. Similarly, intense physical activity at work can produce anxiety for workers, despite leisure time physical activity having benefits on mental health which also displays a dose-response relationship ⁶³. Whatever the mode of active commuting to and from work, it might follow the same logic with high intensities not necessarily having the strongest benefits – even in the model using crude or less adjusted hazard ratio.

4.4 Walking and cycling for active commuting

Walking at a brisk/fast pace demonstrated a stronger reduction of all-cause, cardiovascular or cancer mortality compared with walking at a slower pace ⁶⁴, we report for the first-time similar benefits of walking (of up to 41%, depending on level of active commuting and type of mortality) during active commuting to or from work. Being bipedal is an intrinsic characteristic within the evolution of human beings ⁶⁵. Furthermore, walking is free ⁶⁶ and can provide social connections ⁶⁷. Moreover, walking has strong psychological and mental health benefits ⁶⁸. Being more relaxed when arriving at work may also have economic advantages for companies ⁶⁹. Reduction of mortality is also related to active commuting by cycling (up to 33%). We also demonstrated a dose-response relationship for walking, but the reduction of mortality provided by active commuting by cycling follows more of a U shape. However, we can note that when both walking and cycling were assessed in the same study ¹⁴, adding cycling to walking seemed more protective. Since there is a win-win relationships for workers and companies whatever the type of active commuting (a healthy worker is a more profitable worker) ⁷⁰, it would be

necessary to encourage the installation of showers in the workplace to promote active commuting in general, and to permit active commuting at a high level for those who are willing cycle or walk to work. Infrastructure should also include other facilities such as changing rooms, lockers or bicycle garages. Some companies and government departments have experimented with allocation of incentives/bonuses to workers actively commuting to and from the workplace ⁷¹.

4.5 Limitations and Strengths

Our study has some limitations. A limited number of studies were included. However, we included a large sample size of 829 098 workers, promoting the generalisability of our results. Our meta-analysis inherited the limitations of the 17 individual studies that contributed to the study and met the inclusion criteria. Therefore, the study was subjected to the bias of included studies such as the bias of exposure ascertainment and the bias of outcome assessment. Even if all individual studies included in our meta-analyses were excellent and published in very well-known high-quality journals, description of active commuting was mainly self-reported, limiting the quality of the reported data. Conditions of fulfilment (e.g. at home or at work, in occupational medicine departments) were not always reported, which has been shown to influence results from self-reported questionnaires ⁷². Similarly, the level of physical activity was also self-reported by questionnaires. Ideally, a rigorous analysis of intensity should have been adjusted for fitness ⁷³⁻⁷⁵, but measuring heart rate during exercise and performing VO₂ max tests is deemed impossible for such large-scale cohort studies. While most studies attempted to assess dose response effects, our groups of levels of physical activity were heterogeneous because of the variability of the parameters retrieved within each included study (intensity ^{13,22}, duration per day ^{8,9,16,36,37} or week ^{10,39}, MET-hour/week ^{11,41,42}, or frequency ¹²). However, mortality was assessed mainly with the use of National mortality databases

guaranteeing accuracy of data. All included studies had a prospective cohort design. Though there were similarities between the populations' characteristics within each included article were not identical. Although data were collected in several countries, emerging countries are not represented. Moreover, the majority of studies were conducted in Europe ^{7-10,13,14,16,36,37,39,40}, with only one study from the United-States ³⁸, one from Japan ¹² and one from China ¹¹. However, all ethnicities were included ¹⁴. Generalisability of our results may also suffer from some single-site studies ^{7,9,10,12,16,39,40}, even if half of the included studies were multi-site ^{8,11,13,14,36-38}. We computed sensitivity analyses (data not shown) demonstrating similar results whatever the study design. Even if having more effect sizes within each meta-analysis than constituent studies that can be found in several articles published in high ranked journals ^{76,77}, our meta-analysis followed a rigorous methodology and only once did we include the same population in our meta-analysis. We manipulated the different data for the same outcome depending on the adjustment model by computing a meta-analysis using only fully adjusted estimates of risks, and we computed a sensitivity analyses based on crude or less adjusted risks. Therefore, the weight of studies did not require further ponderings ⁷⁸. Moreover, Egger's test was non-significant highlighting the absence of major publication bias. A major limitation of our meta-analysis is the lack of data on characteristics of workers because several studies were part of larger cohorts evaluating the effects of physical activity in general. However, the fact that most included studies assessed leisure physical activity to adjust risk calculation, limits bias of confusion. This was the case even if leisure physical activity was assessed on self-reported questionnaires – as well as for active commuting. Most studies adjusted risk calculations based on adequate models considering several putative confounding factors and included workers representative of the general population. However, we noted that no article adjusted risk calculation on pre-existing illness. Causality should also be discussed as a

limitation in the context of observational studies. Another limitation is the absence of significant results from meta-regressions.

5 Conclusion

We demonstrated that active commuting decreases mainly all-cause and cardiovascular mortality, with a dose response relationship, especially for walking. Preventive strategies should focus on the benefits of active commuting.

Data Availability Statement

All relevant data are included within this article and its Electronic supplementary material.

Compliance with Ethical Standards

Funding

No sources of funding were used to assist in the preparation of this article.

Conflicts of interests

Frédéric Dutheil, Séverine Pélangéon, Martine Duclos, Philippe Vorilhon, Martial Mermillod, Julien S Baker, Bruno Pereira and Valentin Navel declare that they have no conflicts of interest relevant to the content of this review.

Author contributions

Frédéric Dutheil conceived and designed the analysis. Frédéric Dutheil, Séverine Pélangéon and Valentin Navel conducted the systematic literature search. Frédéric Dutheil, Séverine Pélangéon, Martine Duclos, Philippe Vorilhon, Martial Mermillod, Julien Baker, Bruno Pereira and Valentin Navel gave final approval for the eligibility of all articles included in the analysis and provided critical revision of the article. Frédéric Dutheil and Bruno Pereira analysed the data. Séverine Pélangéon and Frédéric Dutheil wrote the first draft of the manuscript and were responsible for the integrity of the data analysis.

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Figures Legends

Fig 1. Flow Diagram according with PRISMA Guidelines

Fig 2. Methodological quality of included articles using Newcastle – Ottawa Quality Assessment Scale

For each item, criteria fulfilled: No: 0, Yes: 1 (*: 2 subitems), Unclear: ?, Not applicable: NA

Fig 3. Summary of meta-analysis showing the effects of active commuting by type of mortality (all cause, cardiovascular and cancer mortality), by type of active commuting (walking, cycling or both), by level of active commuting, by level of active commuting by walking, and by level of active commuting by cycling, based on data from adjusted hazard ratio

Fig 4. Meta-analysis showing the effects of active commuting by type of mortality (all cause, cardiovascular and cancer mortality), based on data from adjusted hazard ratio

Fig 5. Meta-analysis showing the effects of active commuting by level of active commuting, based on data from adjusted hazard ratio

Fig. 1 Flow diagram according to PRISMA guidelines

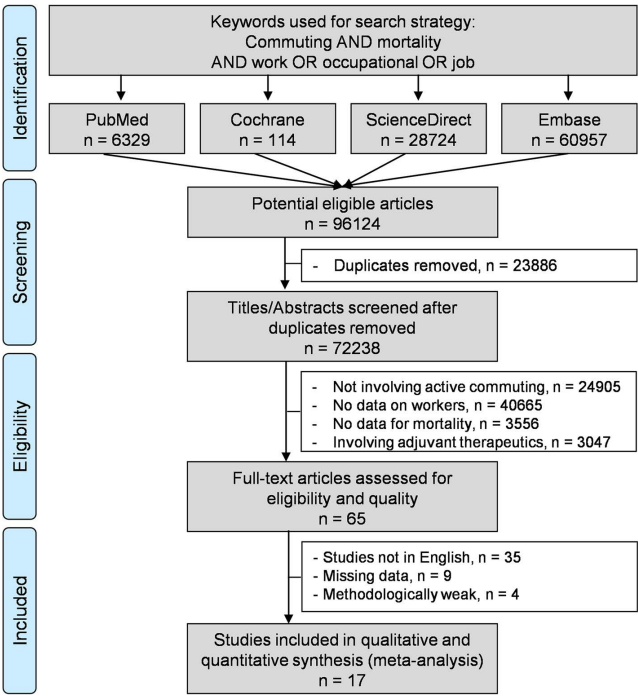


Fig. 2 Methodological quality of included articles using Newcastle—Ottawa Quality Assessment Scale. For each item, criteria fulfilled: No: 0, Yes: 1 (*: 2 subitems), Unclear: ?, Not applicable: NA

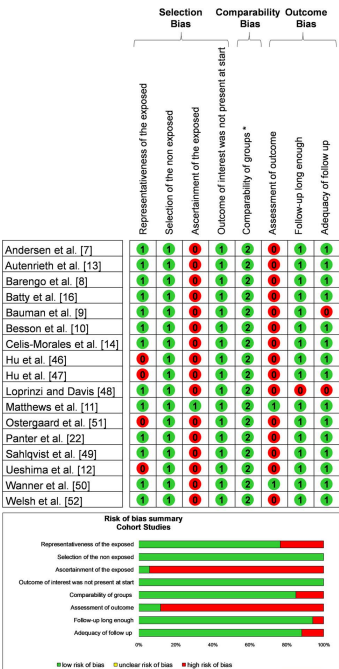
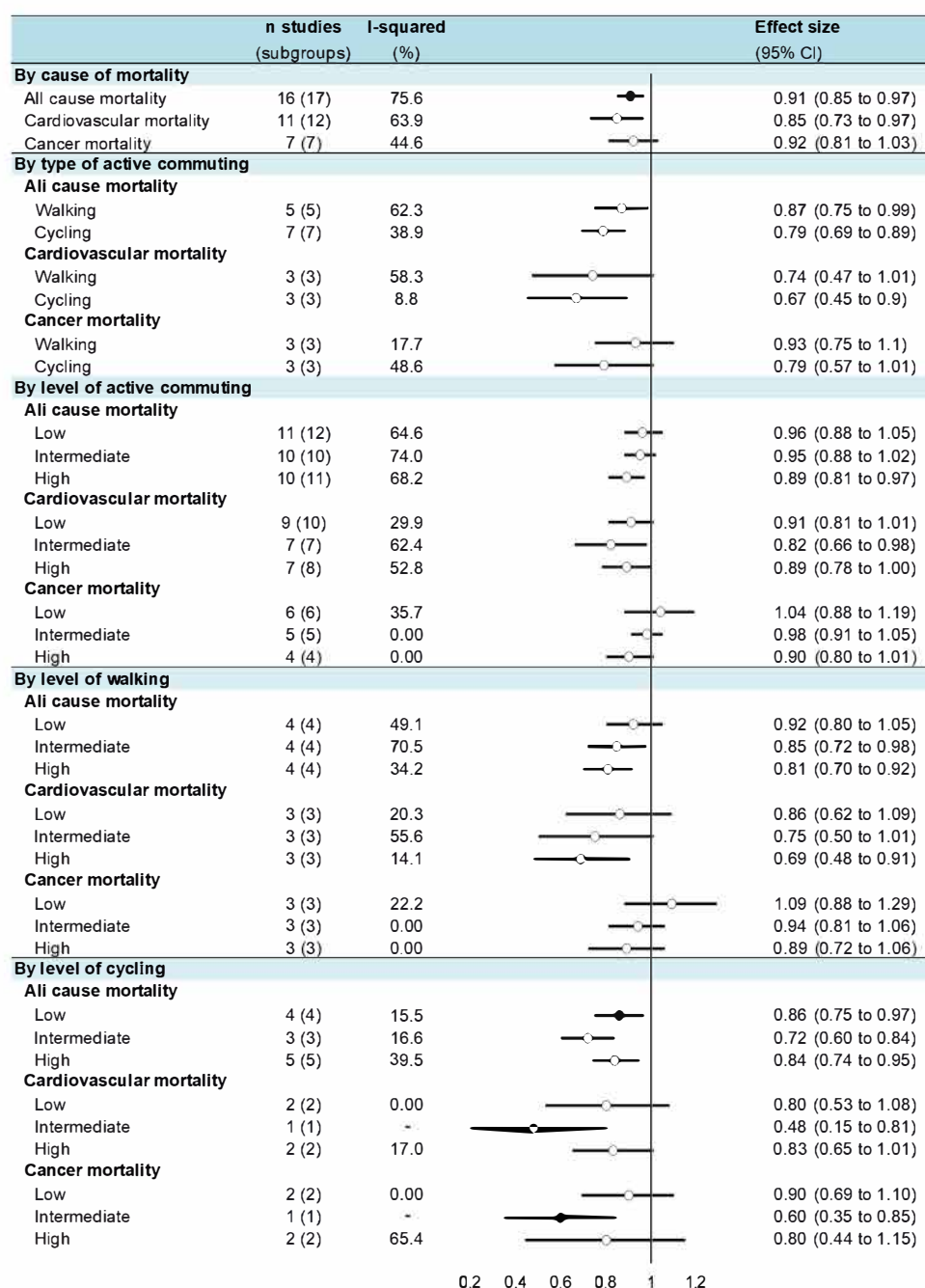


Fig. 3 Summary of meta-analysis showing the effects of active commuting by type of mortality (all cause, cardiovascular and cancer mortality), by type of active commuting (walking, cycling or both), by level of active commuting, by level of active commuting by walking, and by level of active commuting by cycling, based on data from adjusted hazard ratio



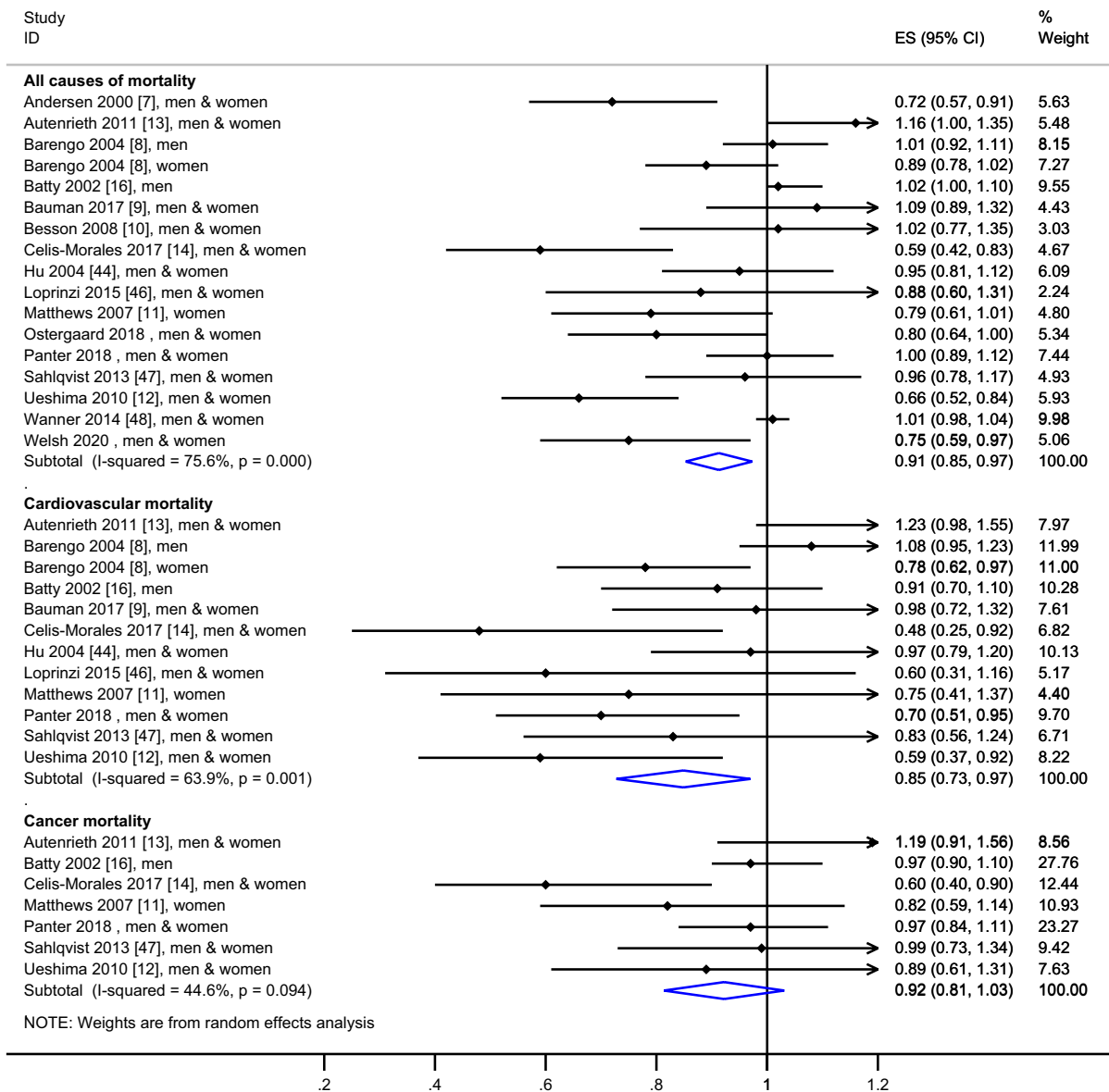


Fig. 4 Meta-analysis showing the effects of active commuting by type of mortality (all cause, cardiovascular and cancer mortality), based on data from adjusted hazard ratio. ES effect size

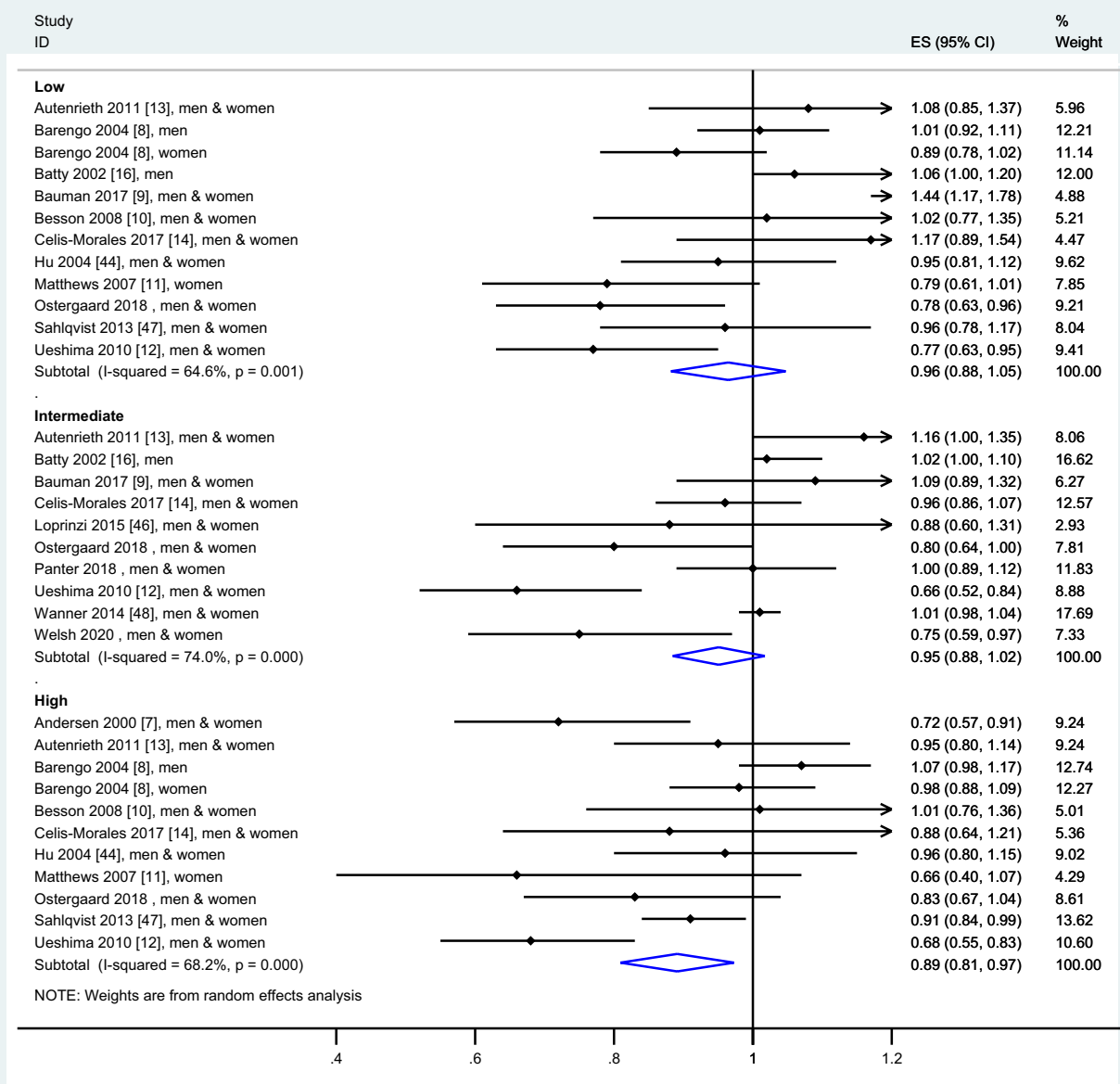


Fig. 5 Meta-analysis showing the effects of active commuting by level of active commuting, based on data from adjusted hazard ratio. *ES* effect size

Electronic Supplementary Material

Electronic Supplementary Material Figure S1. Benefits of active commuting on all-cause mortality stratified by type of commuting – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S2. Benefits of active commuting on cardiovascular mortality stratified by type of commuting – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S3. Benefits of active commuting on cancer mortality stratified by type of commuting – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S4. Benefits of active commuting on all-cause mortality stratified by level of active commuting – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S5. Benefits of active commuting on cardiovascular mortality stratified by level of active commuting – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S6. Benefits of active commuting on cancer mortality stratified by level of active commuting – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S7. Benefits of active commuting by walking on all-cause mortality – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S8. Benefits of active commuting by walking on cardiovascular mortality – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S9. Benefits of active commuting by walking on cancer mortality – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S10. Benefits of active commuting by cycling on all-cause mortality – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S11. Benefits of active commuting by cycling on cardiovascular mortality – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S12. Benefits of active commuting by cycling on cancer mortality – Adjusted Hazard Ratio

Electronic Supplementary Material Figure S13. Funnel plot (meta-funnel), based on data from Adjusted Hazard Ratio

Each dot represents a single study, with its corresponding effect size (x axis) and its associated standard error of the effect estimate (y-axis). Large high-powered studies are placed towards the top, and smaller low-powered studies towards the bottom. The plot should ideally resemble a pyramid or inverted funnel, with scatter due to sampling variation. Studies outside funnel plot are likely to present bias ³³.

Electronic Supplementary Material Figure S14. Summary of meta-analysis showing the effects of active commuting by type of mortality (all cause, cardiovascular and cancer mortality), by type of active commuting (walking, cycling or both), by level of active commuting, by level of active commuting by walking, and by level of active commuting by cycling, based on data from crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S15. Meta-analysis showing the effects of active commuting by type of mortality (all cause, cardiovascular and cancer mortality), based on data from crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S16. Benefits of active commuting on all-cause mortality stratified by type of commuting – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S17. Benefits of active commuting on cardiovascular mortality stratified by type of commuting – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S18. Benefits of active commuting on cancer mortality stratified by type of commuting – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S19. Benefits of active commuting on all-cause mortality stratified by level of active commuting – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S20. Benefits of active commuting on cardiovascular mortality stratified by level of active commuting – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S21. Benefits of active commuting on cancer mortality stratified by level of active commuting – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S22. Benefits of active commuting by walking on all-cause mortality – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S23. Benefits of active commuting by walking on cardiovascular mortality – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S24. Benefits of active commuting by walking on cancer mortality – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S25. Benefits of active commuting by cycling on all-cause mortality – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S26. Benefits of active commuting by cycling on cardiovascular mortality – Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Figure S27. Benefits of active commuting by cycling on cancer mortality – Crude or less adjusted Hazard Ratio

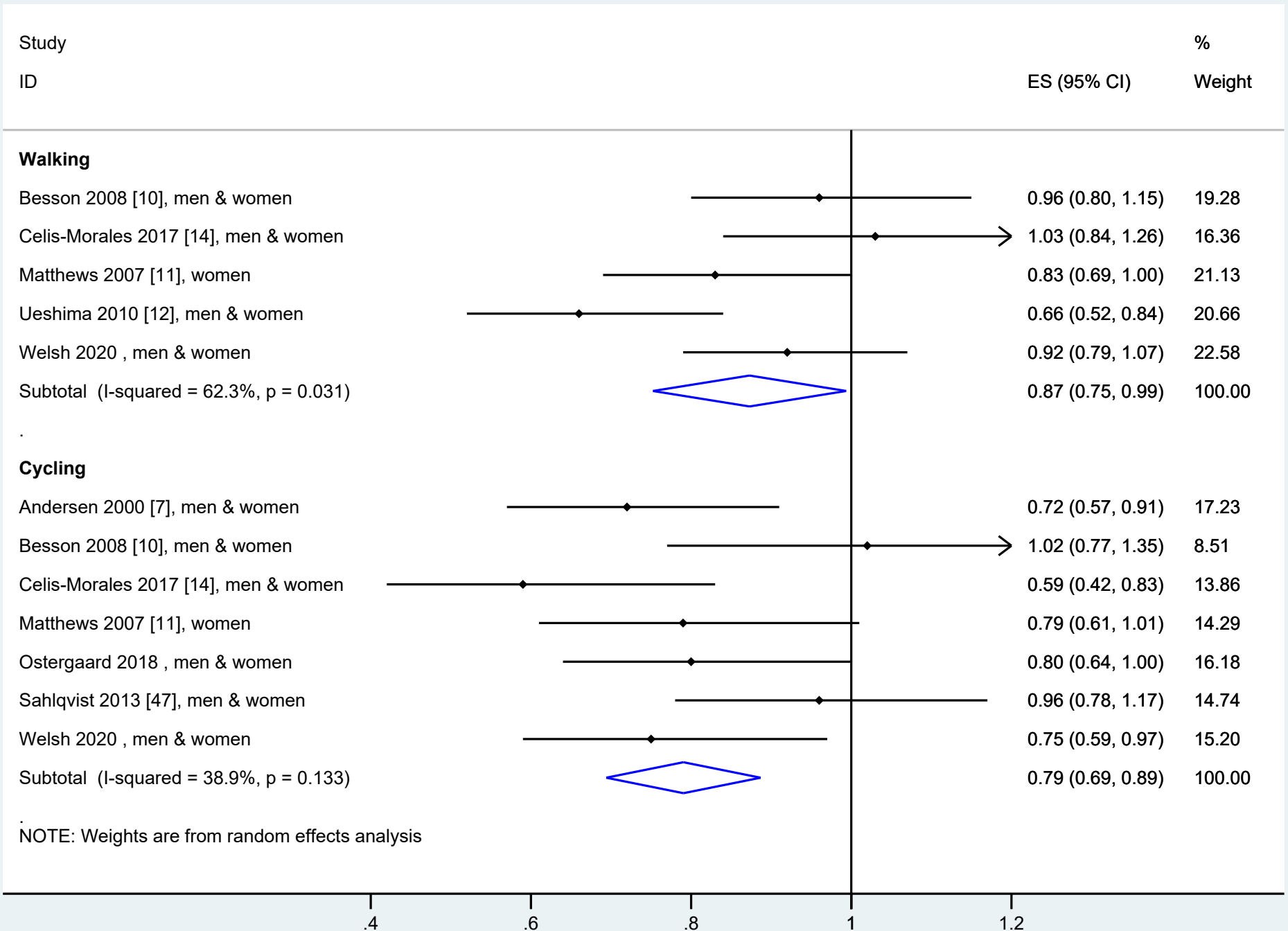
Electronic Supplementary Material Figure S28. Funnel plot (meta-funnel) from Crude or less adjusted Hazard Ratio

Electronic Supplementary Material Appendix S1. Details for the search strategy used within each database.

Electronic Supplementary Material Appendix S2. PRISMA Checklist.

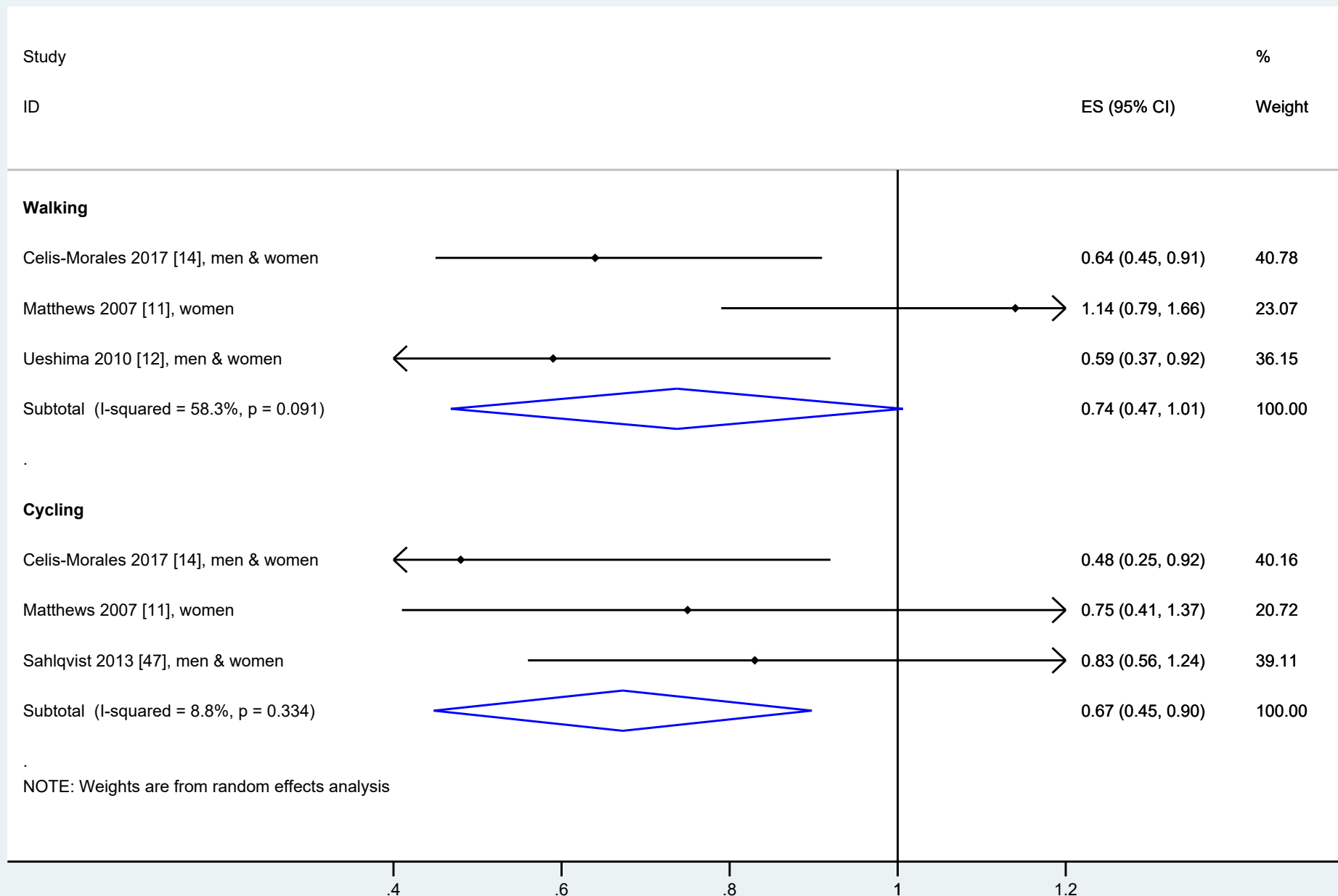
Benefits of active commuting on all-cause mortality

Stratified by type of active commuting - Adjusted hazard ratio



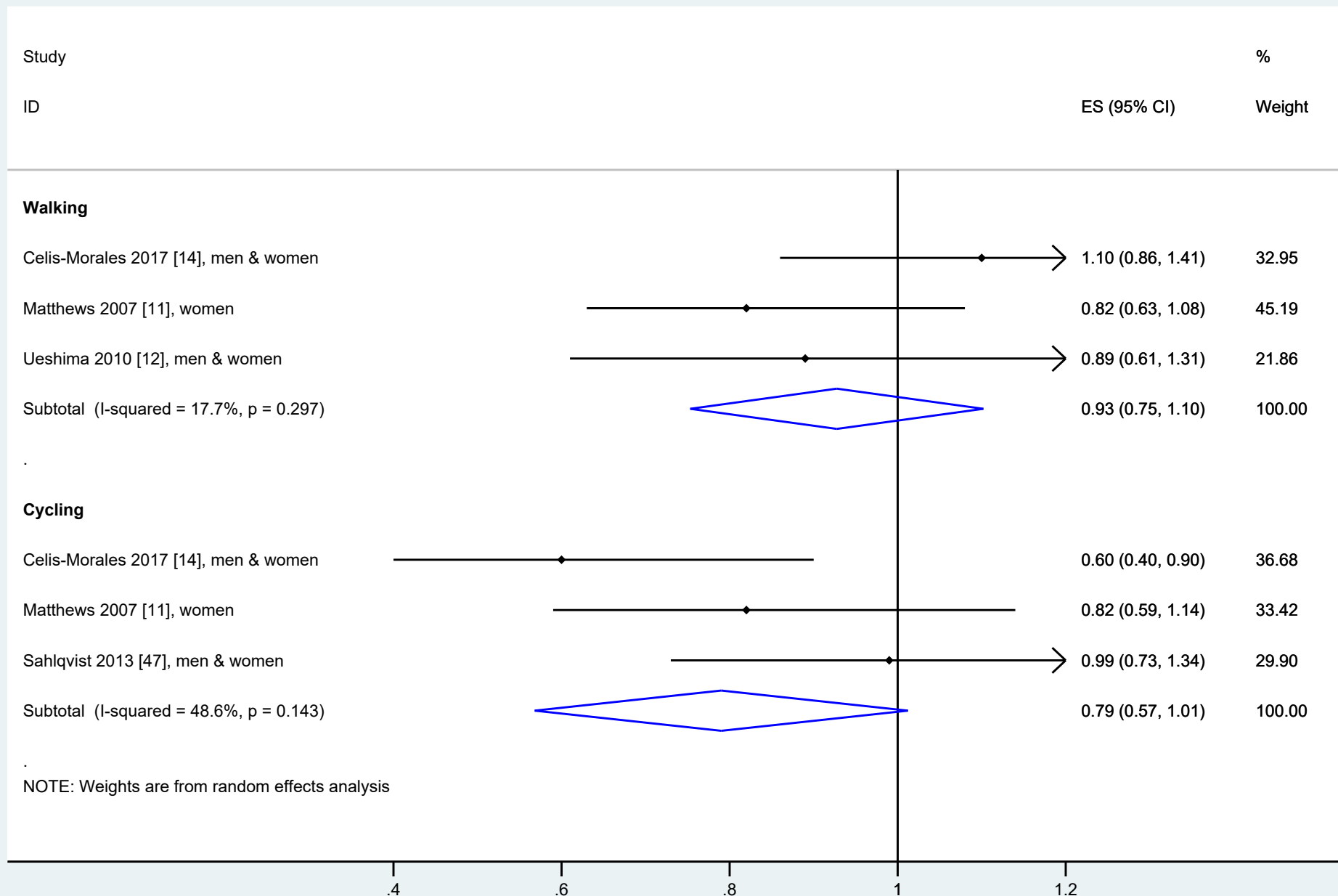
Benefits of active commuting on cardiovascular mortality

Stratified by type of active commuting - Adjusted hazard ratio



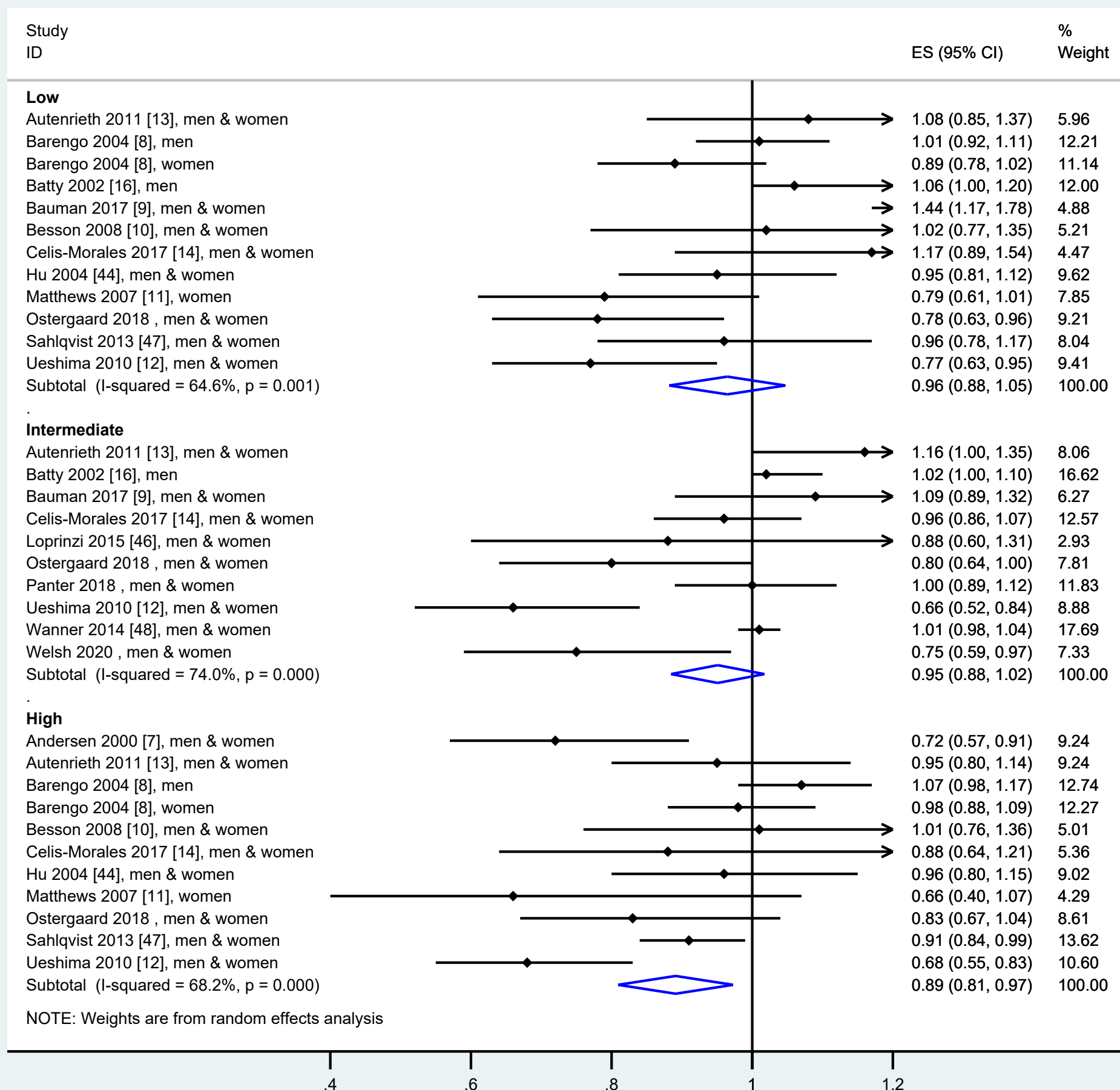
Benefits of active commuting on Cancer mortality

Stratified by type of active commuting - Adjusted hazard ratio



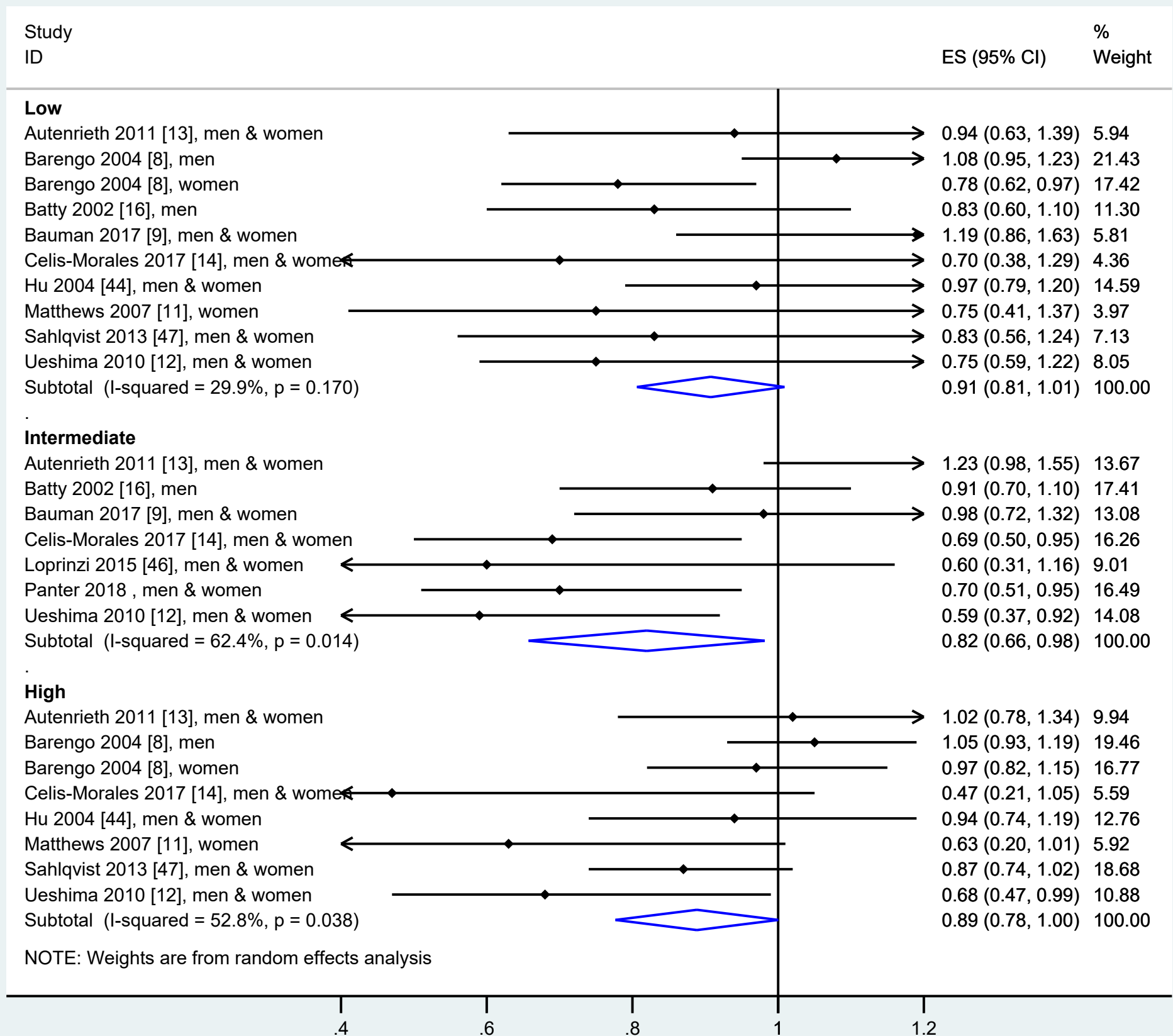
Benefits of active commuting on all-cause mortality

Stratified by level of active commuting - Adjusted hazard ratio



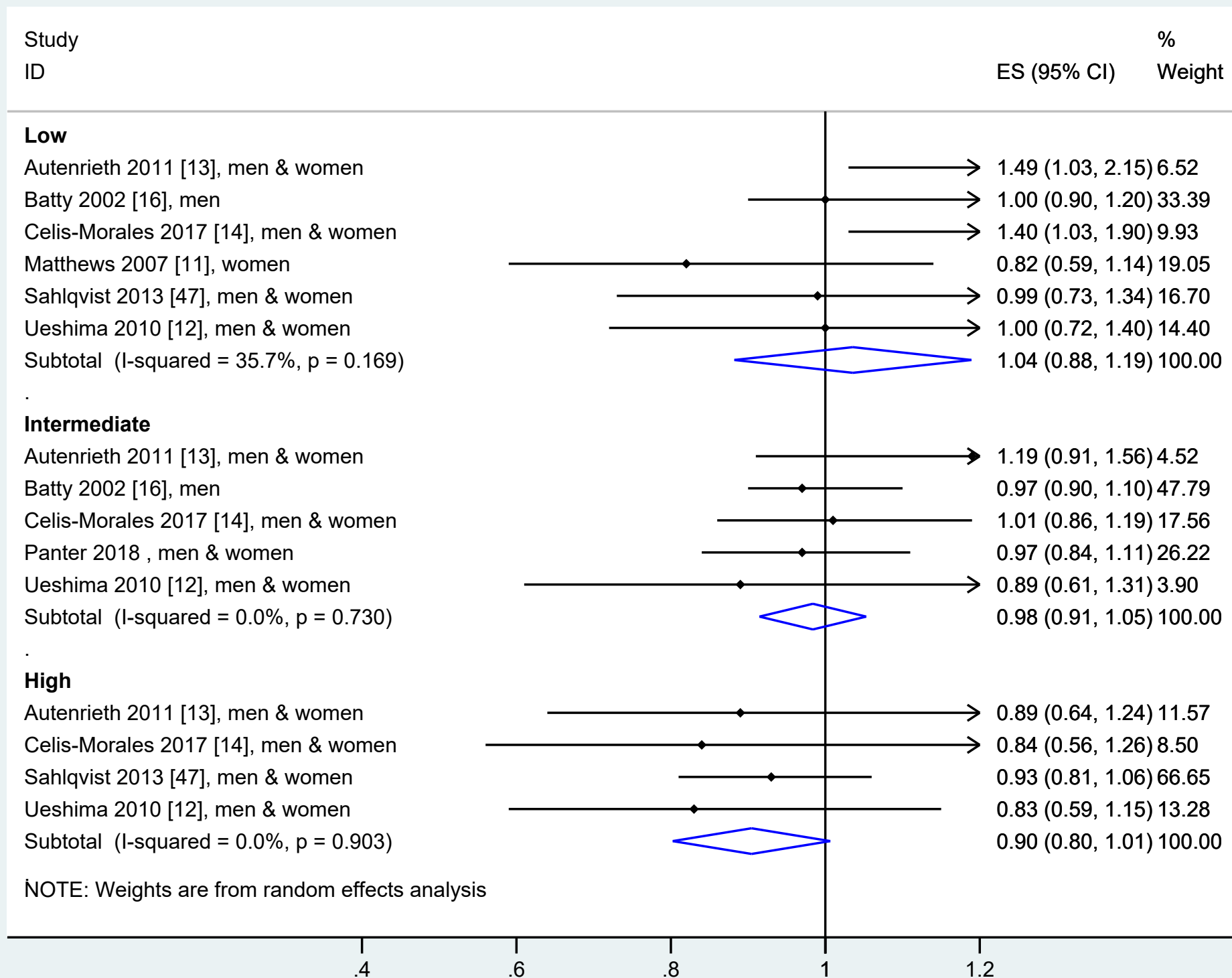
Benefits of active commuting on cardiovascular mortality

Stratified by level of active commuting - Adjusted hazard ratio

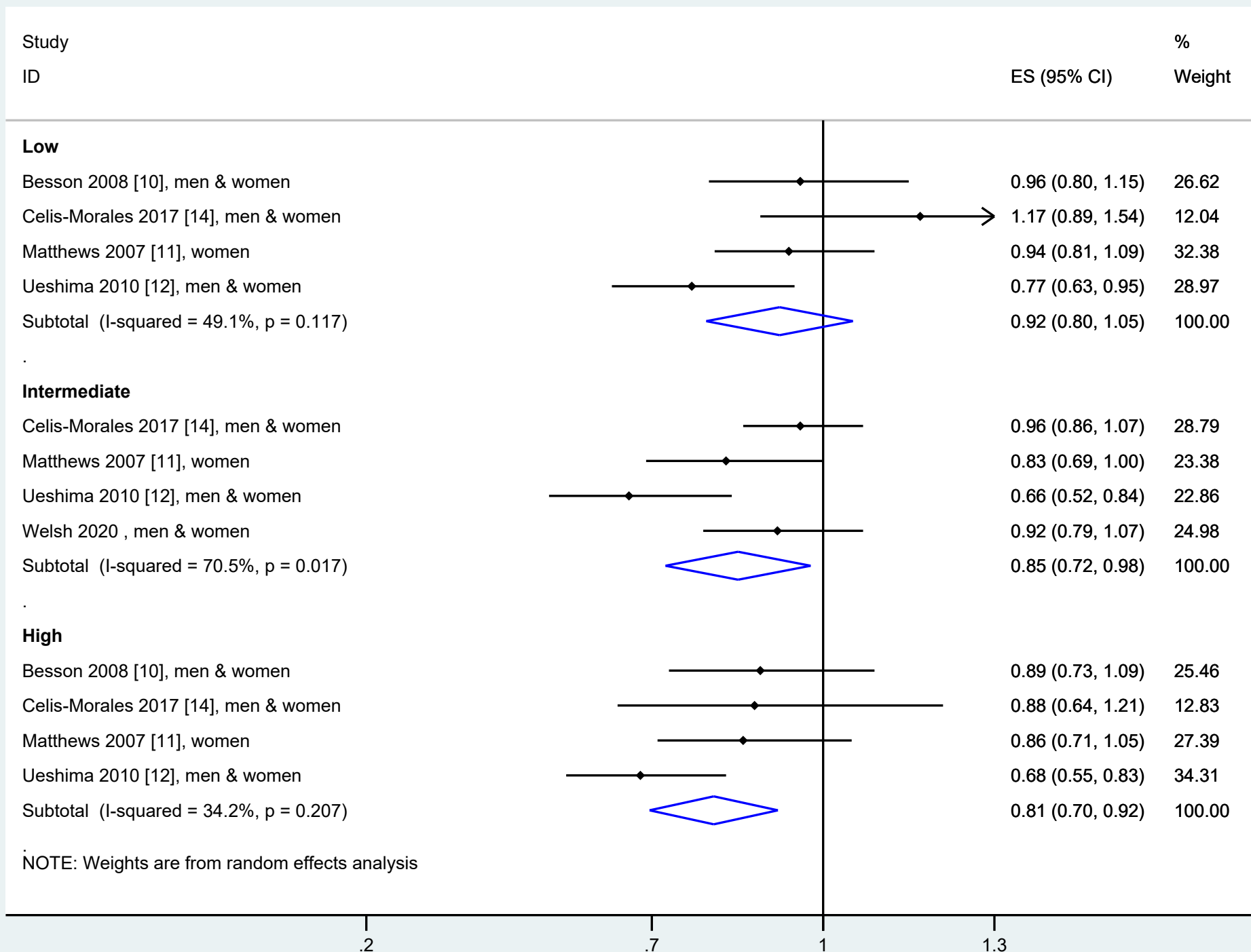


Benefits of active commuting on Cancer mortality

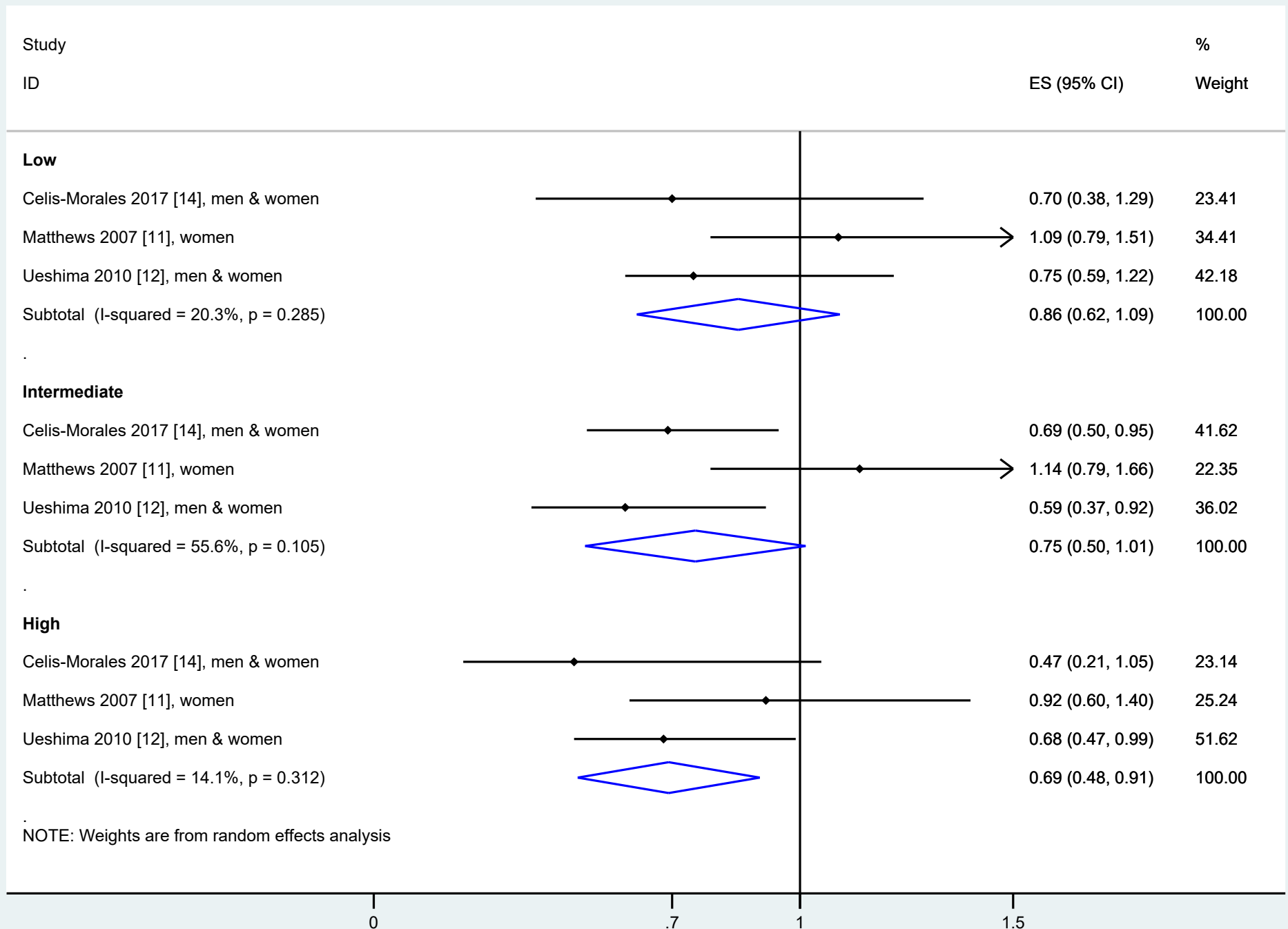
Stratified by level of active commuting - Adjusted hazard ratio



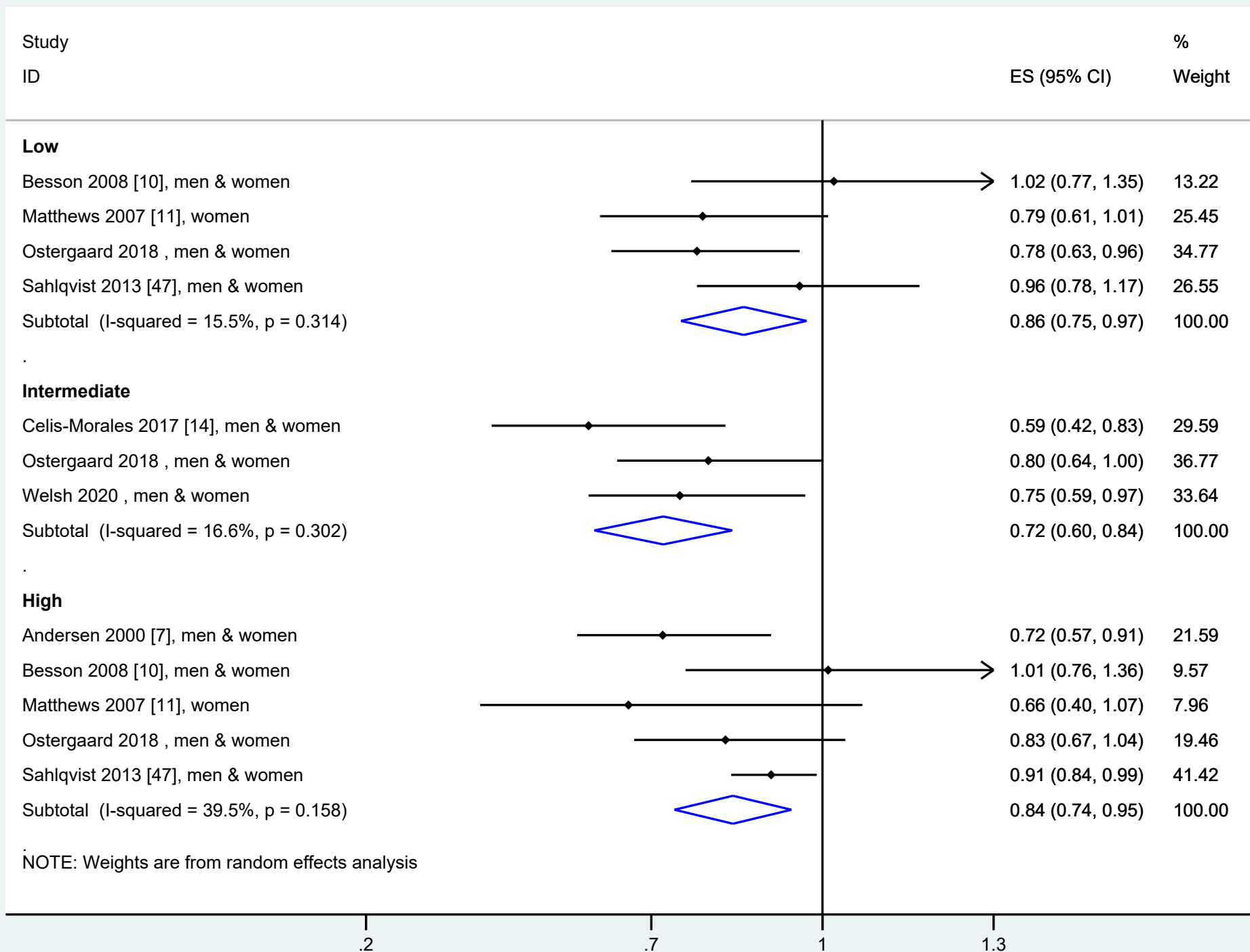
Benefits of active commuting by walking on all-cause mortality - Adjusted hazard ratio



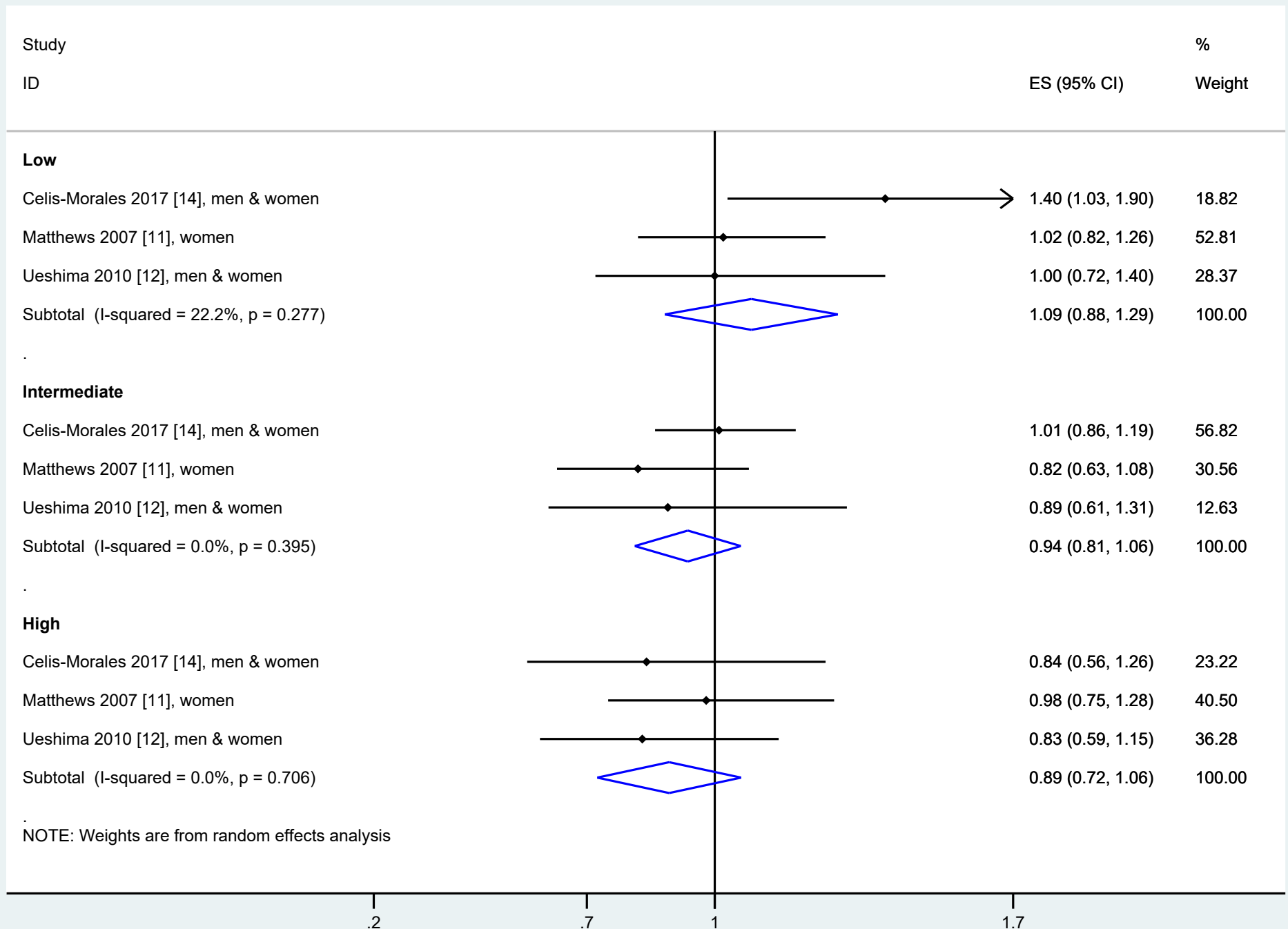
Benefits of active commuting by walking on cardiovascular mortality - Adjusted hazard ratio



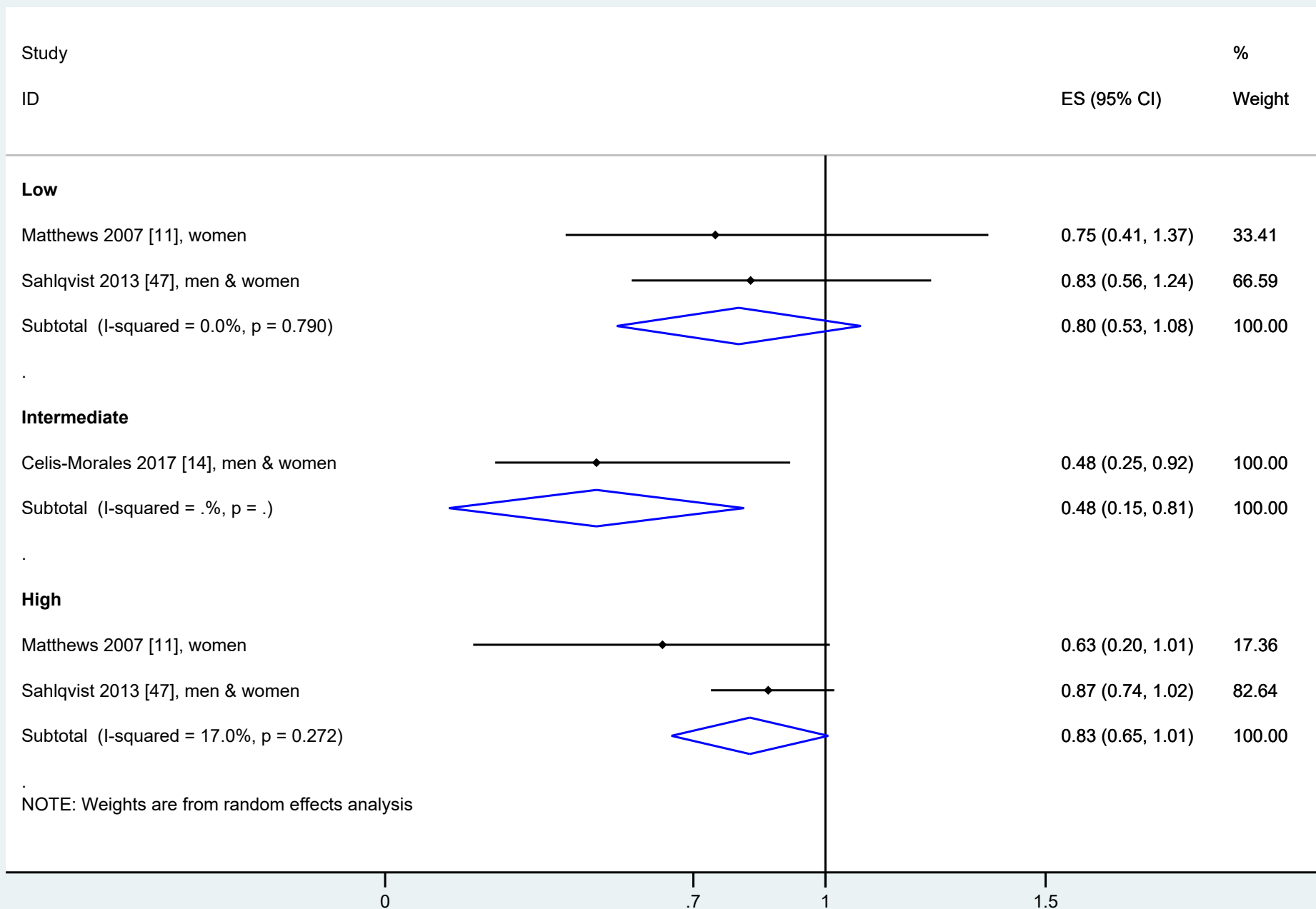
Benefits of active commuting by cycling on all-cause mortality - Adjusted hazard ratio



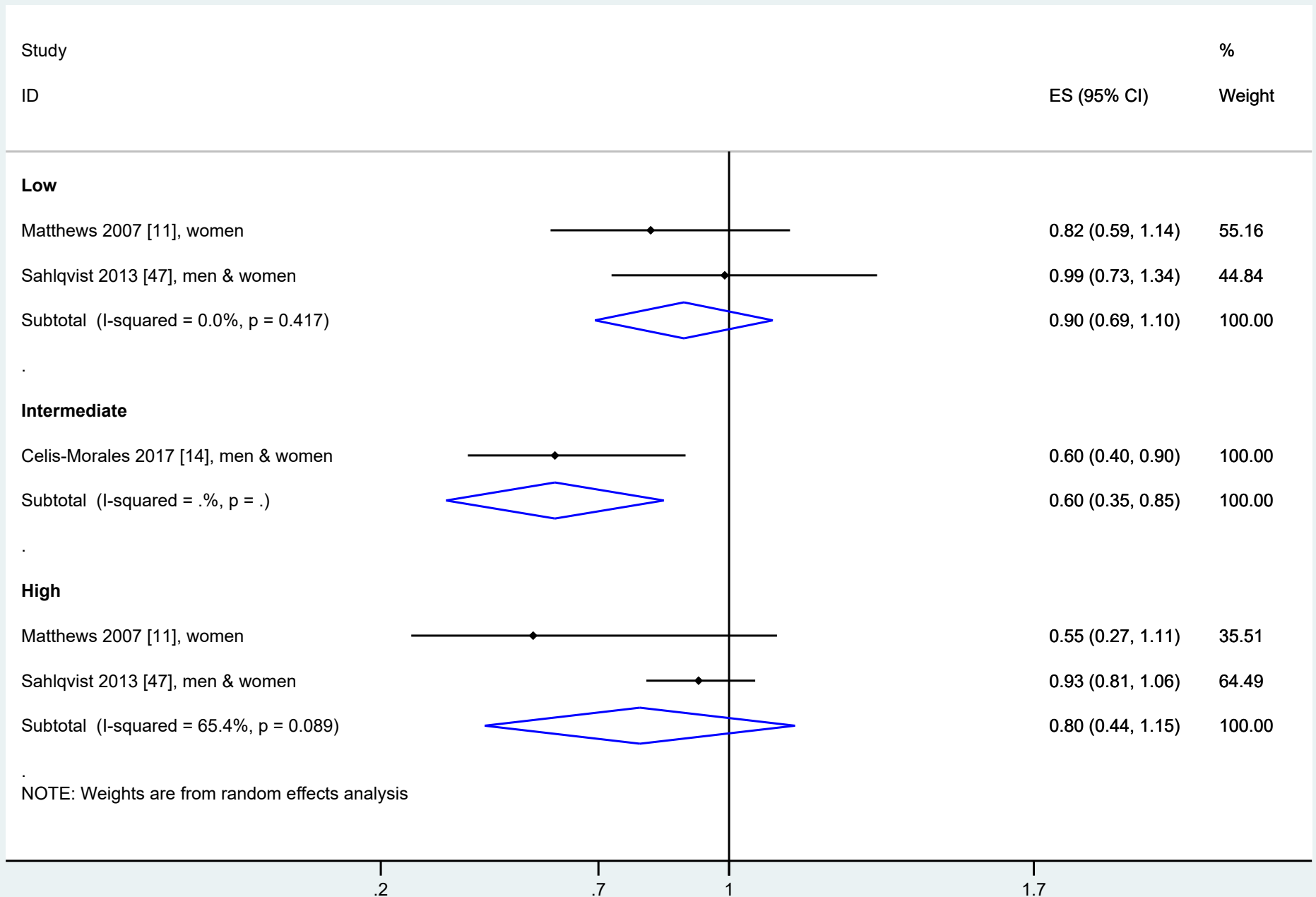
Benefits of active commuting by walking on cancer mortality - Adjusted hazard ratio

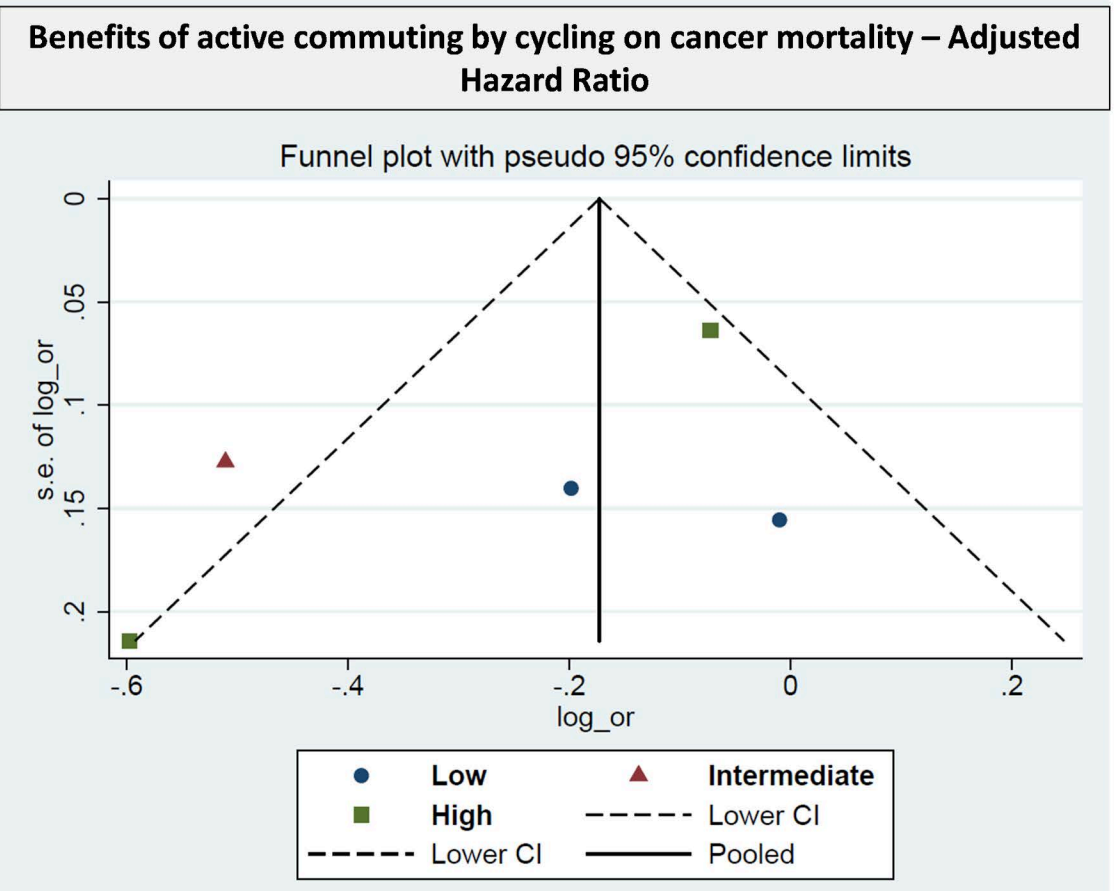
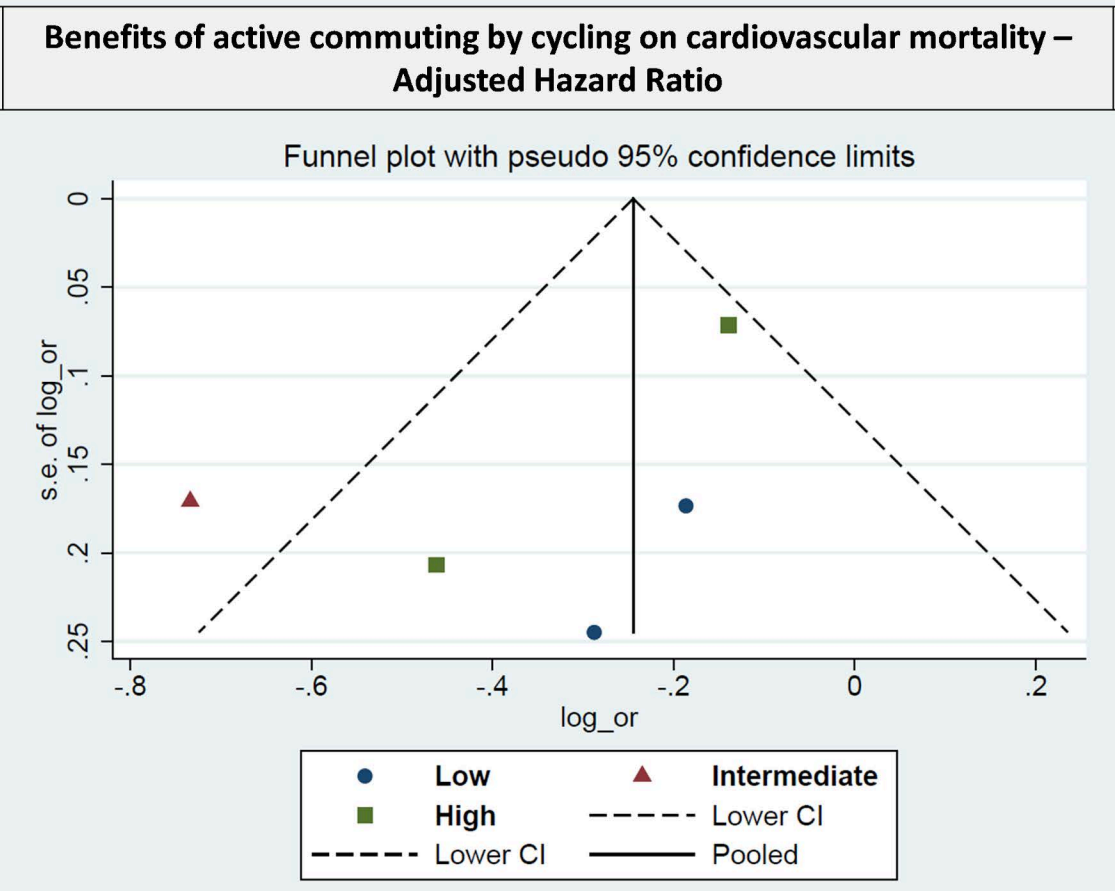
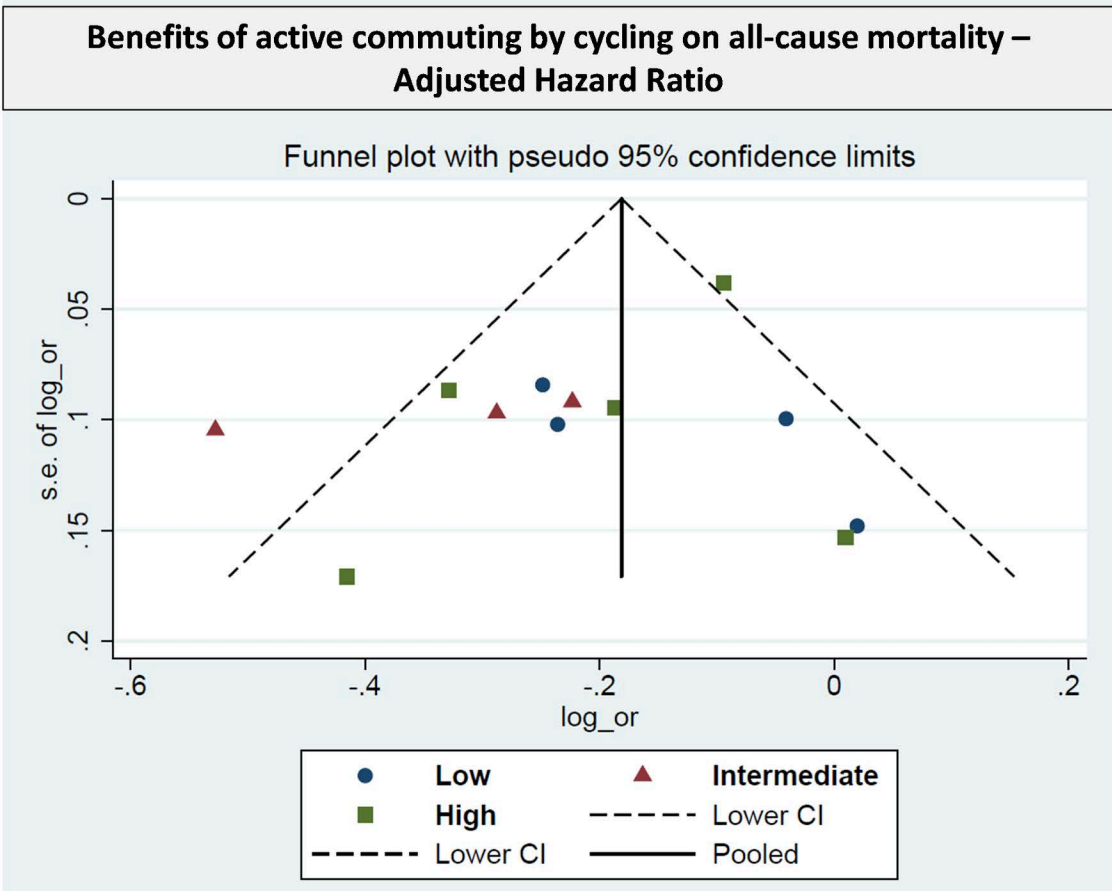
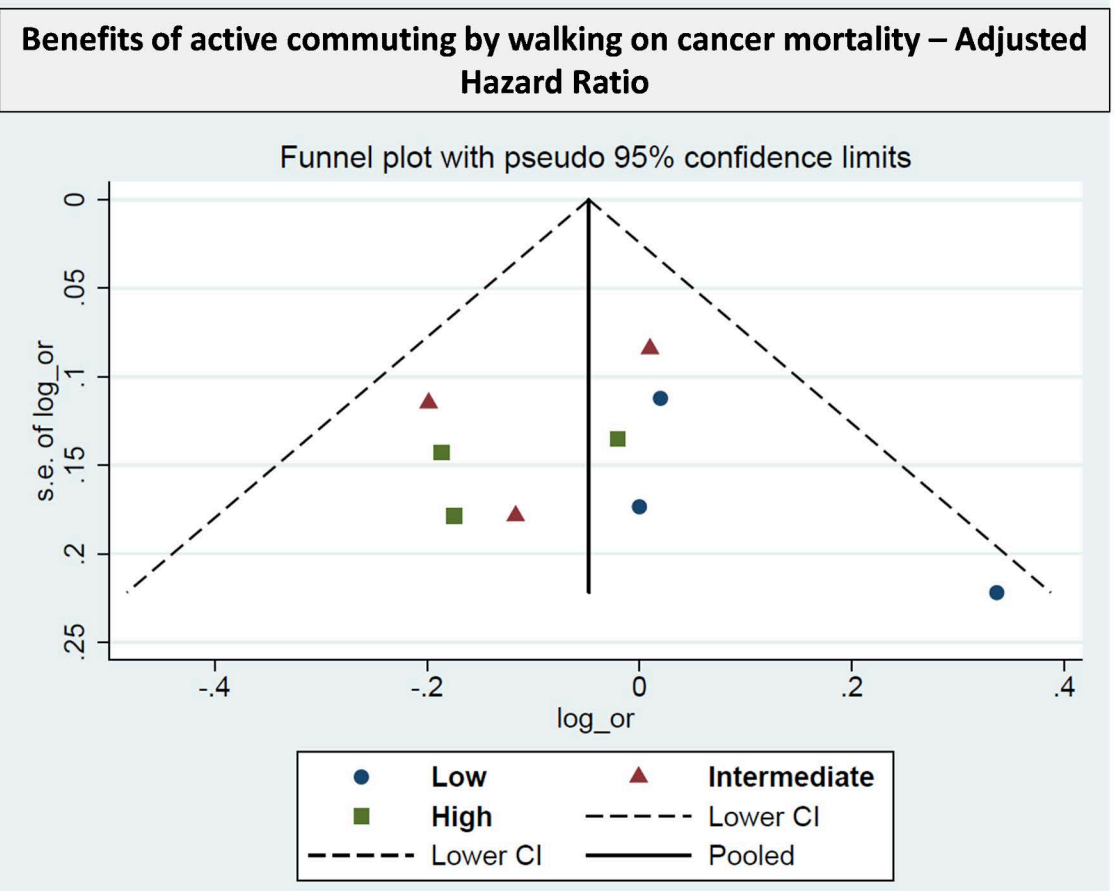
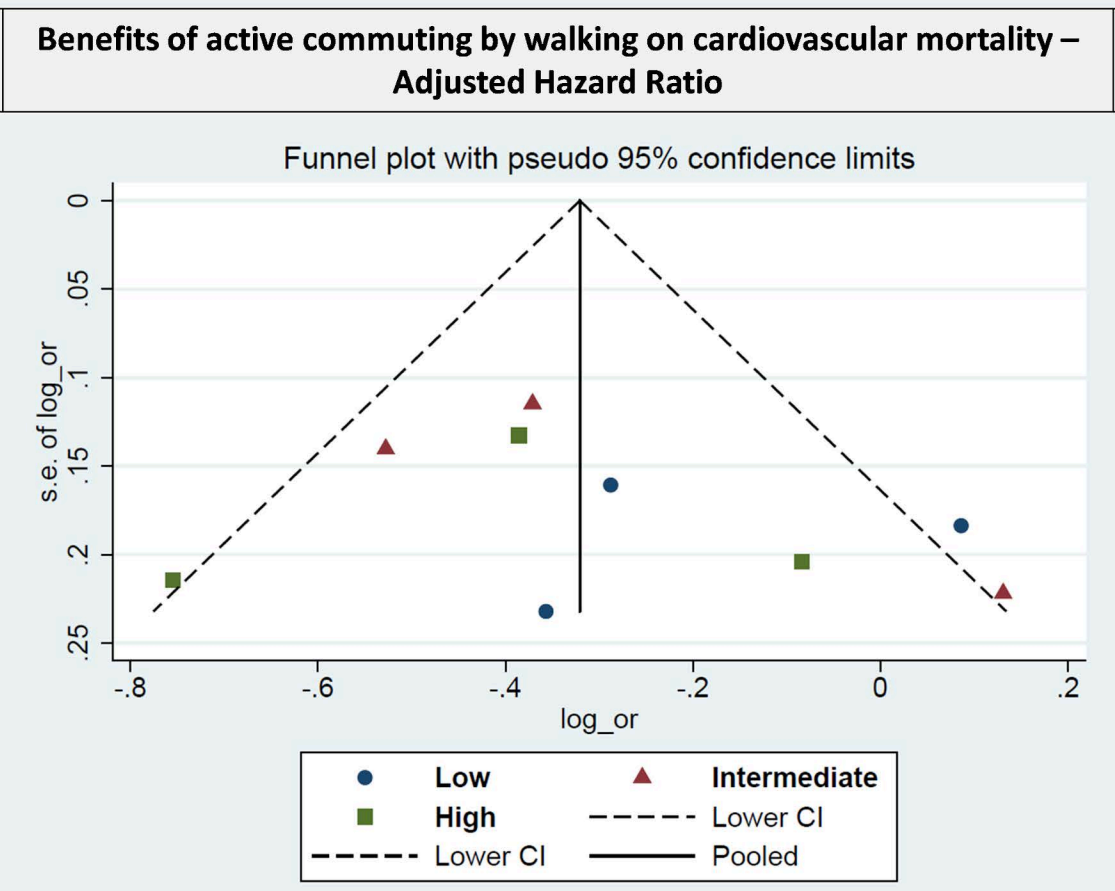
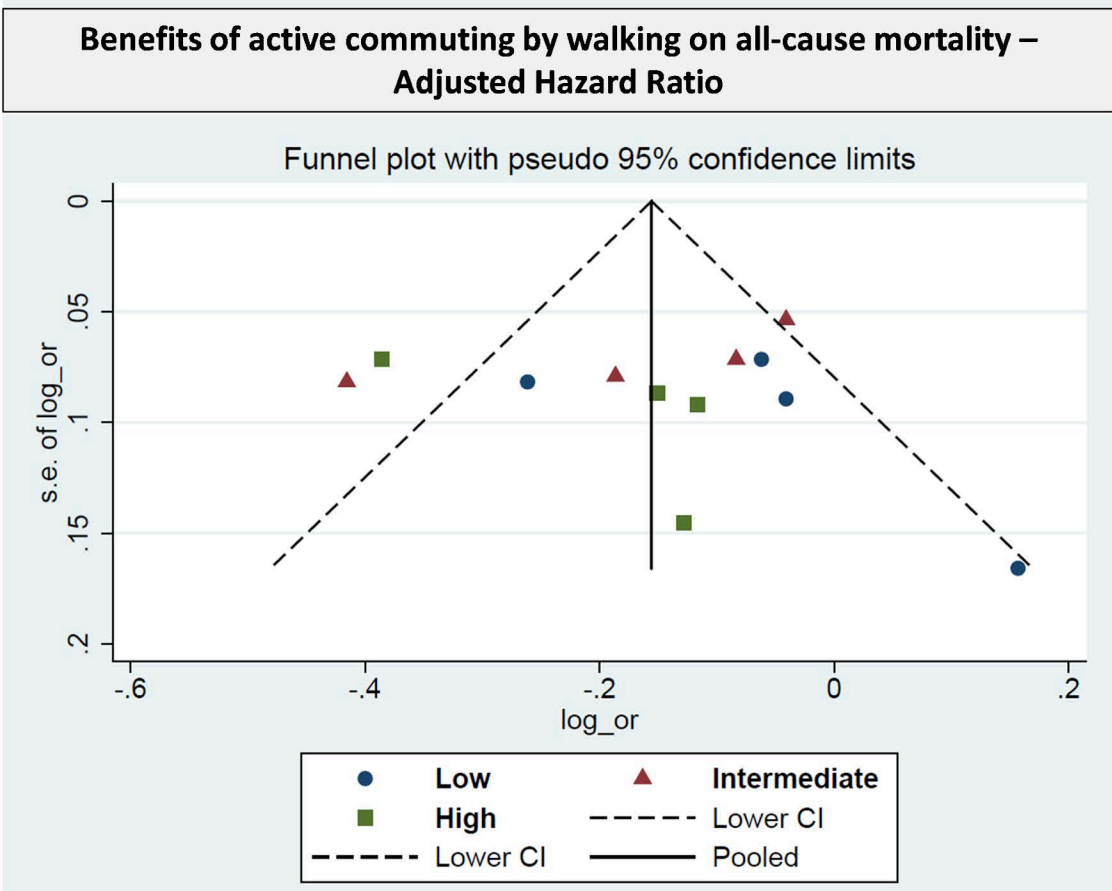
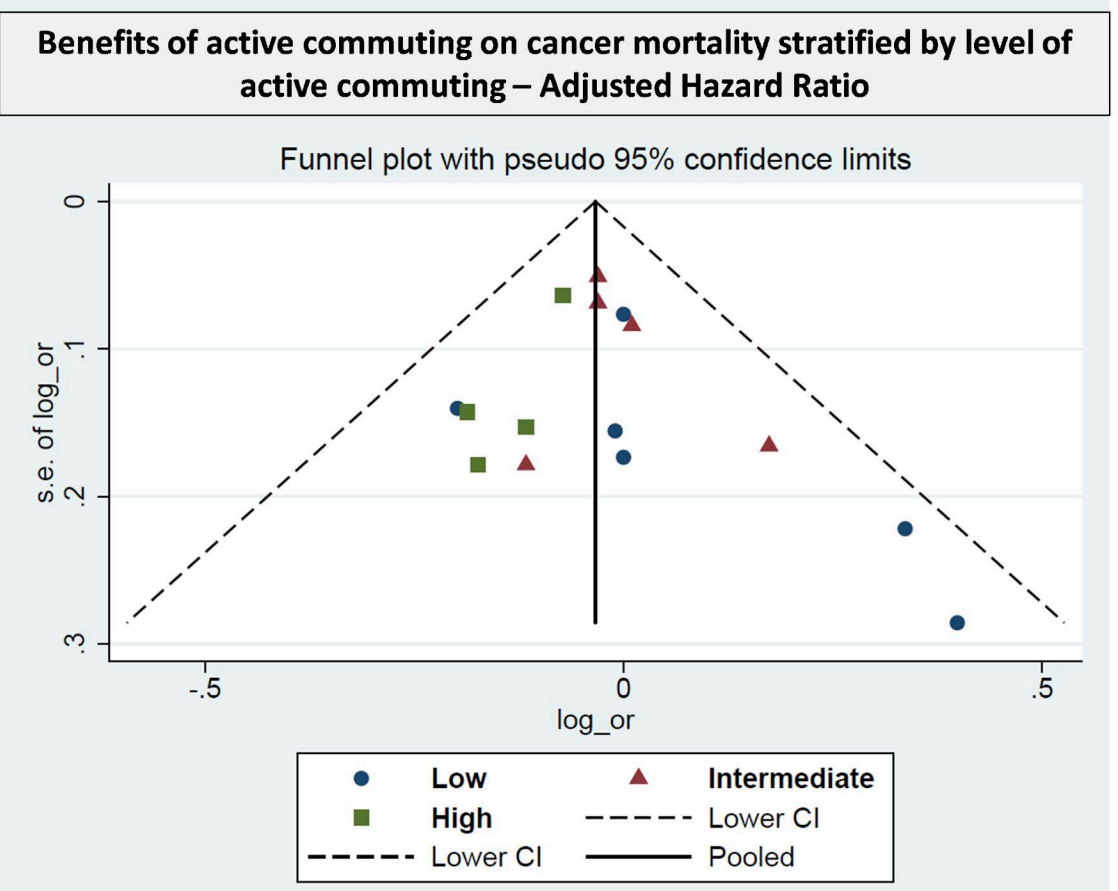
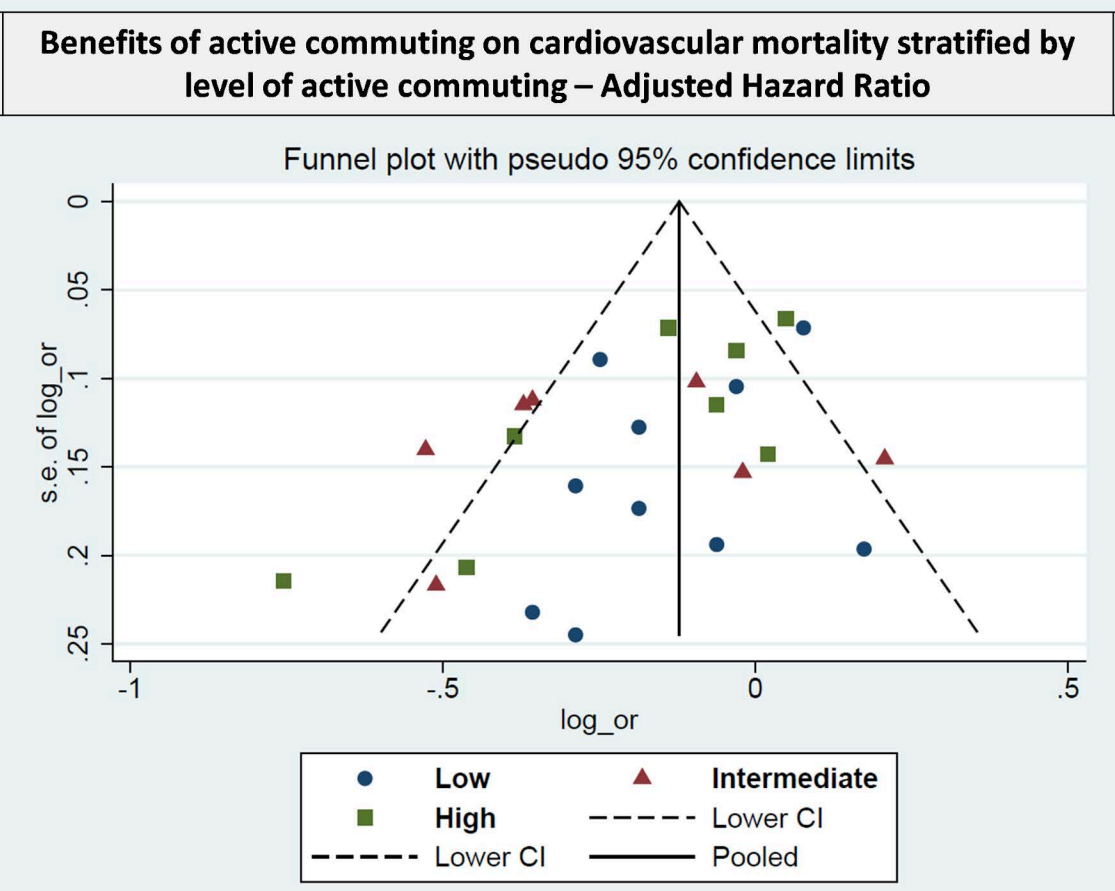
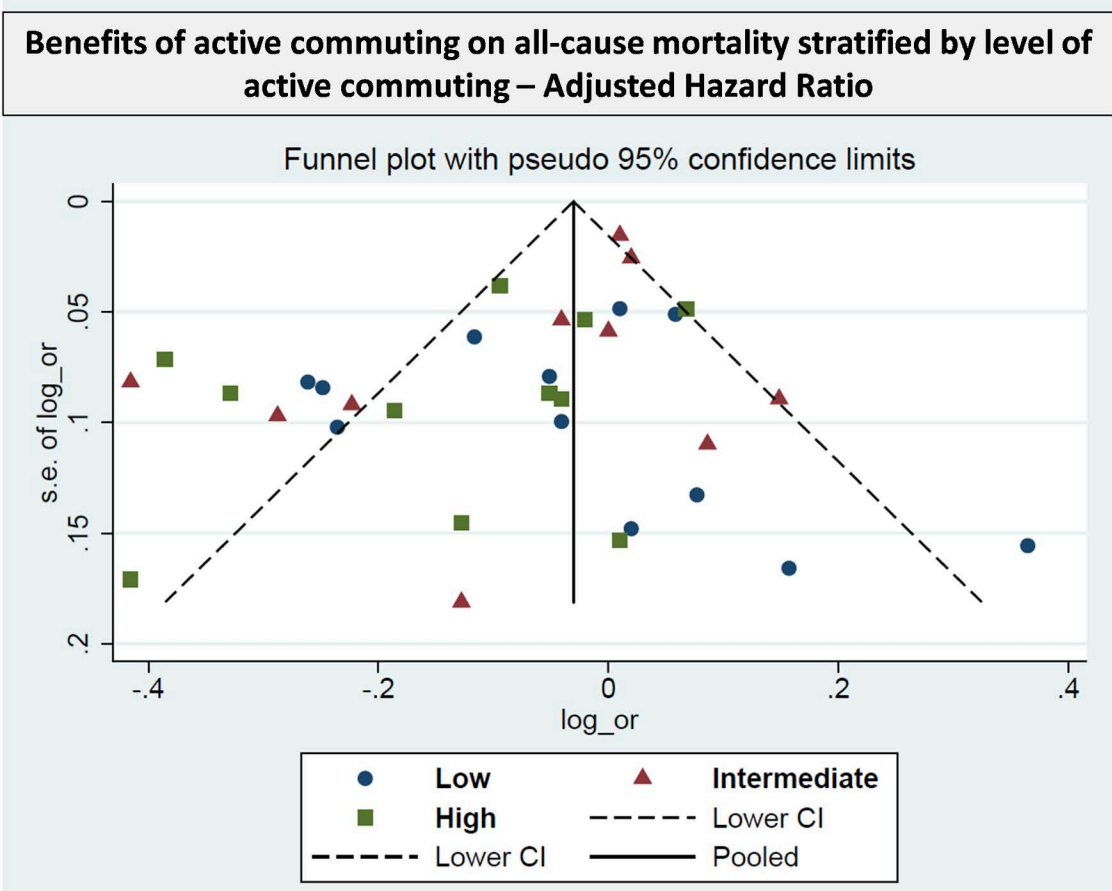
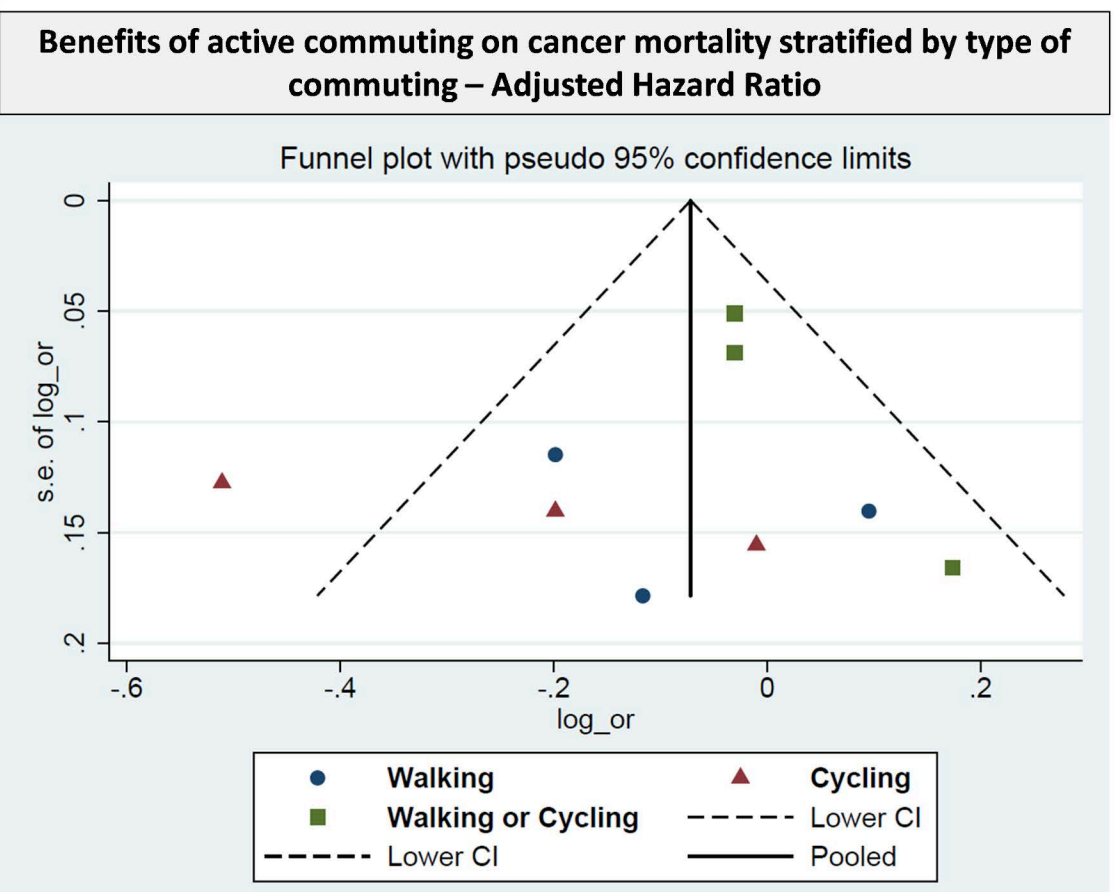
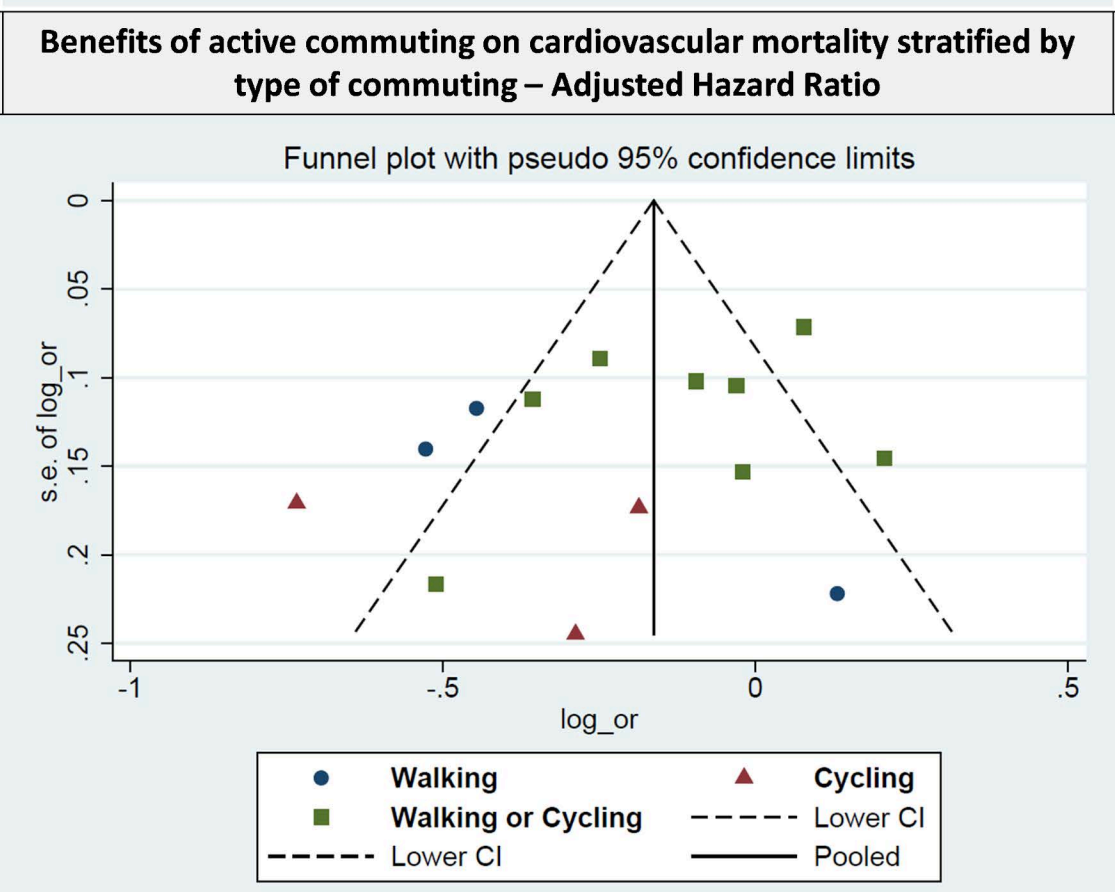
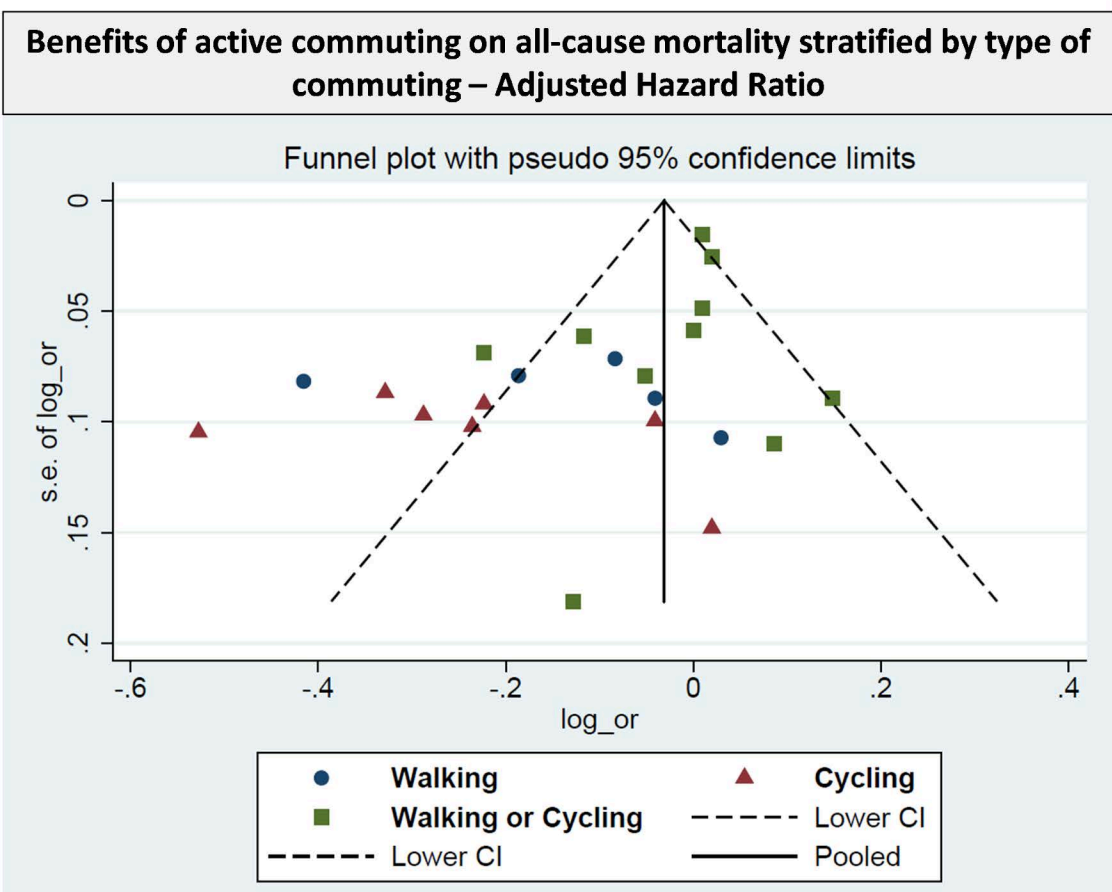
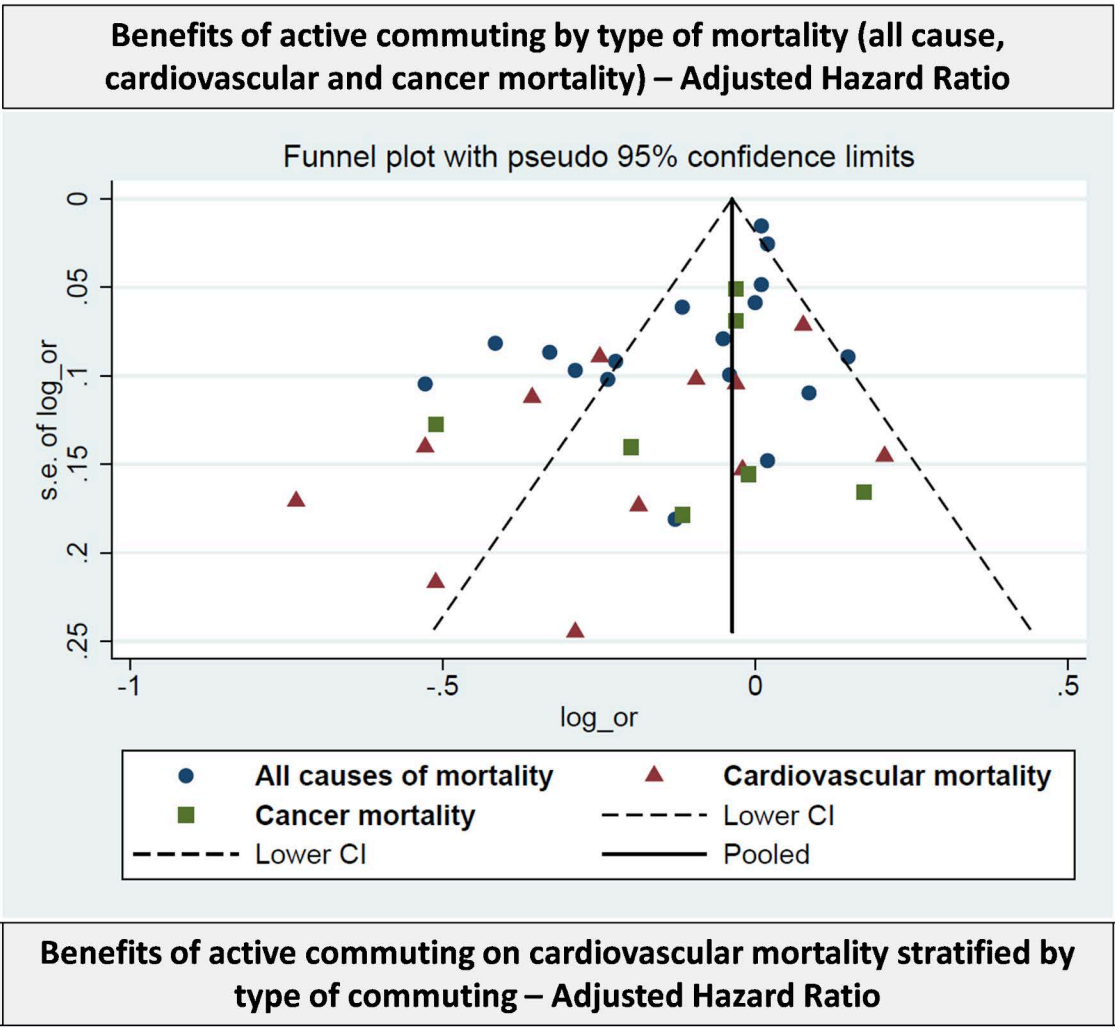


Benefits of active commuting by cycling on cardiovascular mortality - Adjusted hazard ratio



Benefits of active commuting by cycling on cancer mortality - Adjusted hazard ratio

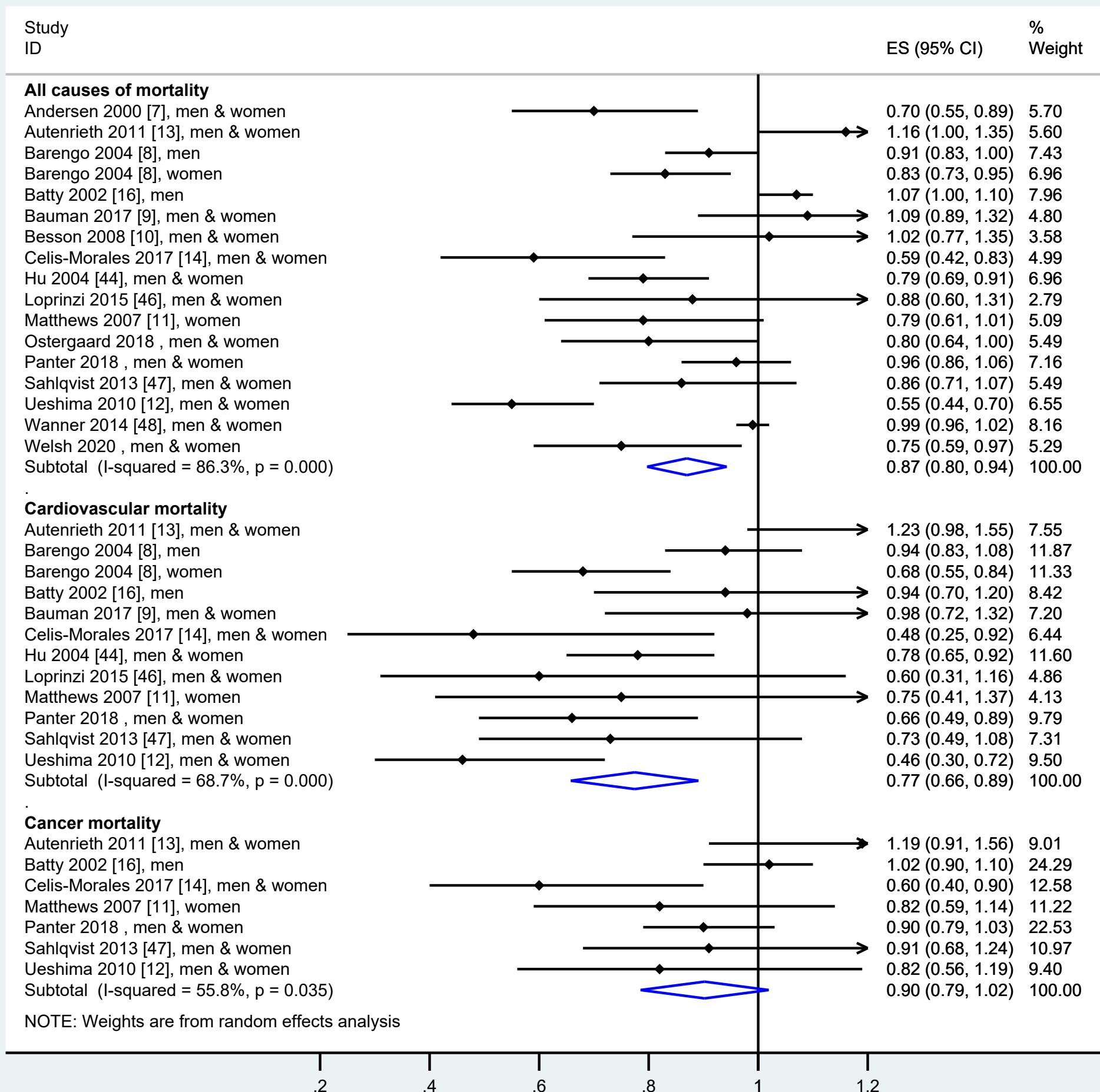




	n studies (subgroups)	I-squared (%)		Effect size (95% CI)
By cause of mortality				
All cause mortality	16 (17)	86.3		0.87 (0.80 to 0.94)
Cardiovascular mortality	11 (12)	68.7		0.77 (0.66 to 0.89)
Cancer mortality	7 (7)	55.8		0.90 (0.79 to 1.02)
By type of active commuting				
All cause mortality				
Walking	5 (5)	83.9		0.85 (0.67 to 1.03)
Cycling	7 (7)	21.2		0.77 (0.69 to 0.85)
Cardiovascular mortality				
Walking	3 (3)	74.1		0.69 (0.38 to 1.00)
Cycling	3 (3)	0.00		0.64 (0.44 to 0.84)
Cancer mortality				
Walking	3 (3)	27.5		0.91 (0.73 to 1.09)
Cycling	3 (3)	30.0		0.77 (0.58 to 0.95)
By level of active commuting				
All cause mortality				
Low	11 (12)	89.2		0.93 (0.82 to 1.05)
Intermediate	10 (10)	87.1		0.93 (0.84 to 1.01)
High	10 (11)	84.9		0.81 (0.71 to 0.92)
Cardiovascular mortality				
Low	9 (10)	38.3		0.81 (0.72 to 0.90)
Intermediate	7 (7)	75.2		0.79 (0.59 to 0.98)
High	7 (8)	75.2		0.75 (0.63 to 0.88)
Cancer mortality				
Low	6 (6)	44.2		1.04 (0.87 to 1.21)
Intermediate	5 (5)	20.7		0.98 (0.90 to 1.06)
High	4 (4)	0.00		0.86 (0.76 to 0.96)
By level of walking				
All cause mortality				
Low	4 (4)	78.0		0.91 (0.72 to 1.09)
Intermediate	4 (4)	88.1		0.82 (0.63 to 1.01)
High	4 (4)	86.6		0.77 (0.54 to 1.00)
Cardiovascular mortality				
Low	3 (3)	53.4		0.80 (0.51 to 1.08)
Intermediate	3 (3)	75.2		0.71 (0.40 to 1.03)
High	3 (3)	52.5		0.59 (0.32 to 0.85)
Cancer mortality				
Low	3 (3)	33.5		1.07 (0.85 to 1.29)
Intermediate	3 (3)	12.4		0.92 (0.78 to 1.05)
High	3 (3)	0.00		0.84 (0.68 to 1.00)
By level of cycling				
All cause mortality				
Low	4 (4)	0.00		0.83 (0.74 to 0.93)
Intermediate	3 (3)	16.6		0.72 (0.60 to 0.84)
High	5 (5)	23.2		0.82 (0.74 to 0.91)
Cardiovascular mortality				
Low	2 (2)	0.00		0.74 (0.48 to 0.99)
Intermediate	1 (1)	-		0.48 (0.15 to 0.81)
High	2 (2)	0.00		0.79 (0.67 to 0.92)
Cancer mortality				
Low	2 (2)	0.00		0.86 (0.67 to 1.06)
Intermediate	1 (1)	-		0.60 (0.35 to 0.85)
High	2 (2)	57.0		0.78 (0.47 to 1.09)
0.2 0.4 0.6 0.8 1 1.2				

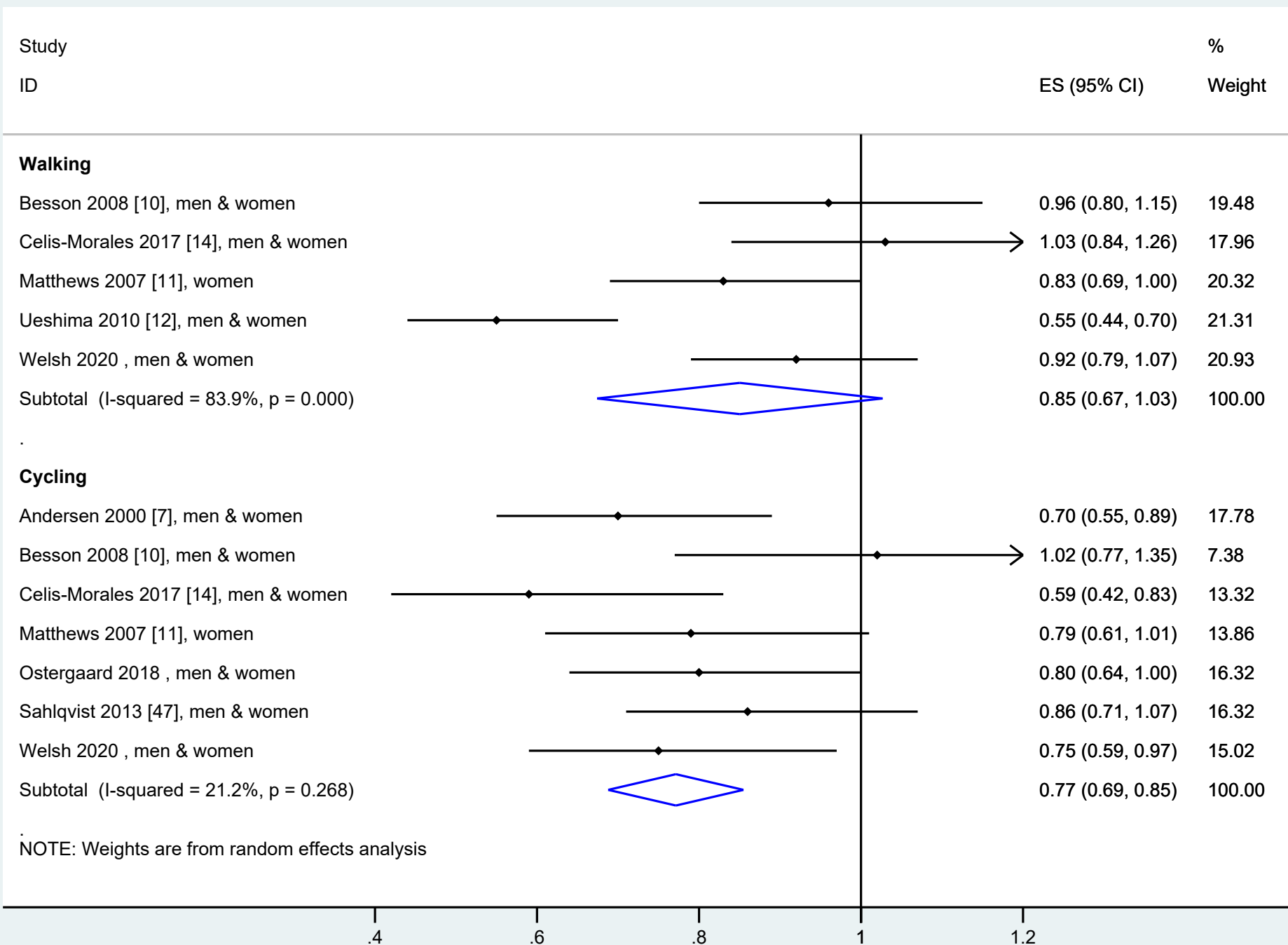
Benefits of active commuting stratified by type of mortality

-- Crude or less adjusted hazard ratio --



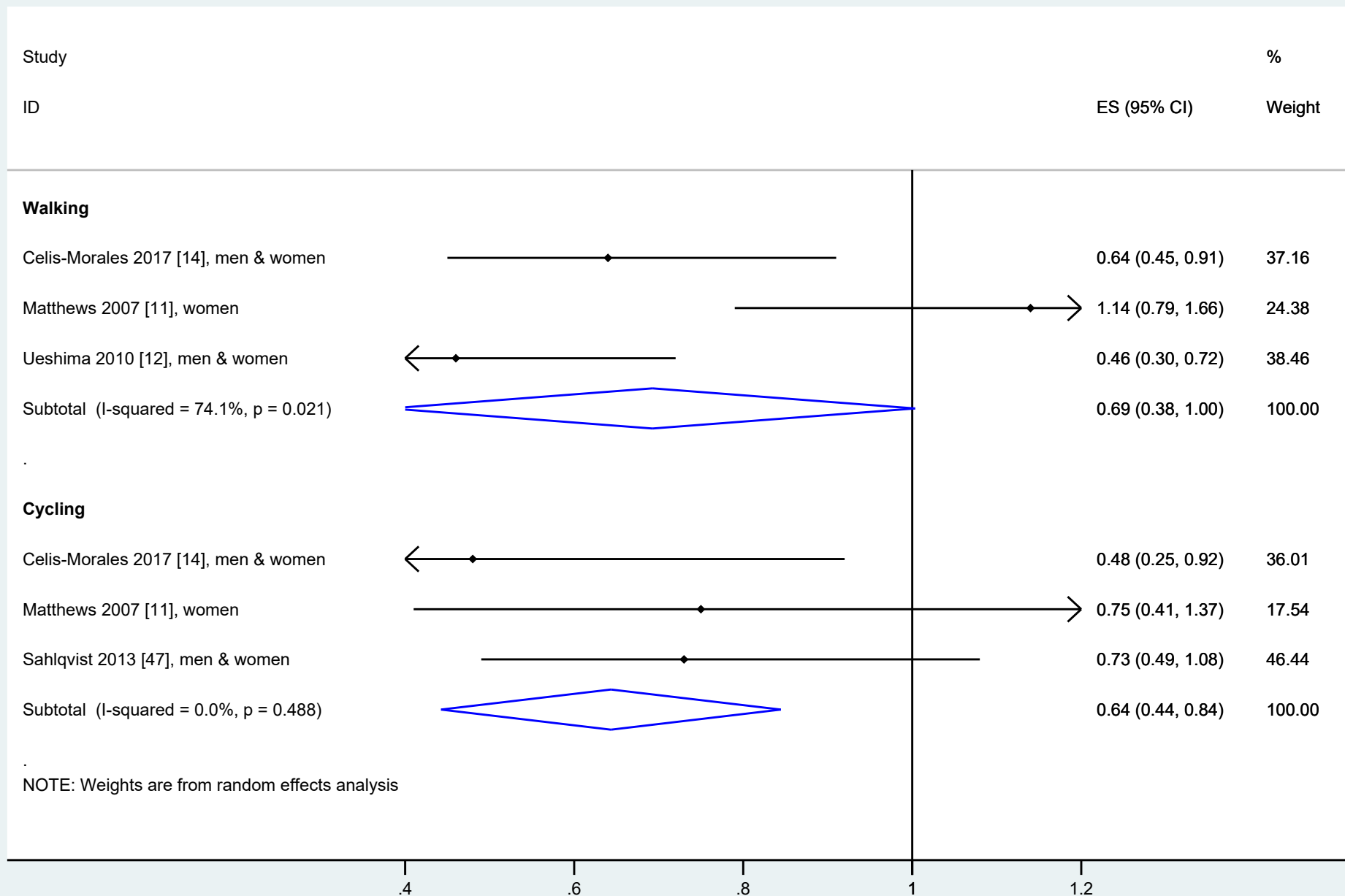
Benefits of active commuting on all-cause mortality

Stratified by type of active commuting - Crude or less adjusted hazard ratio



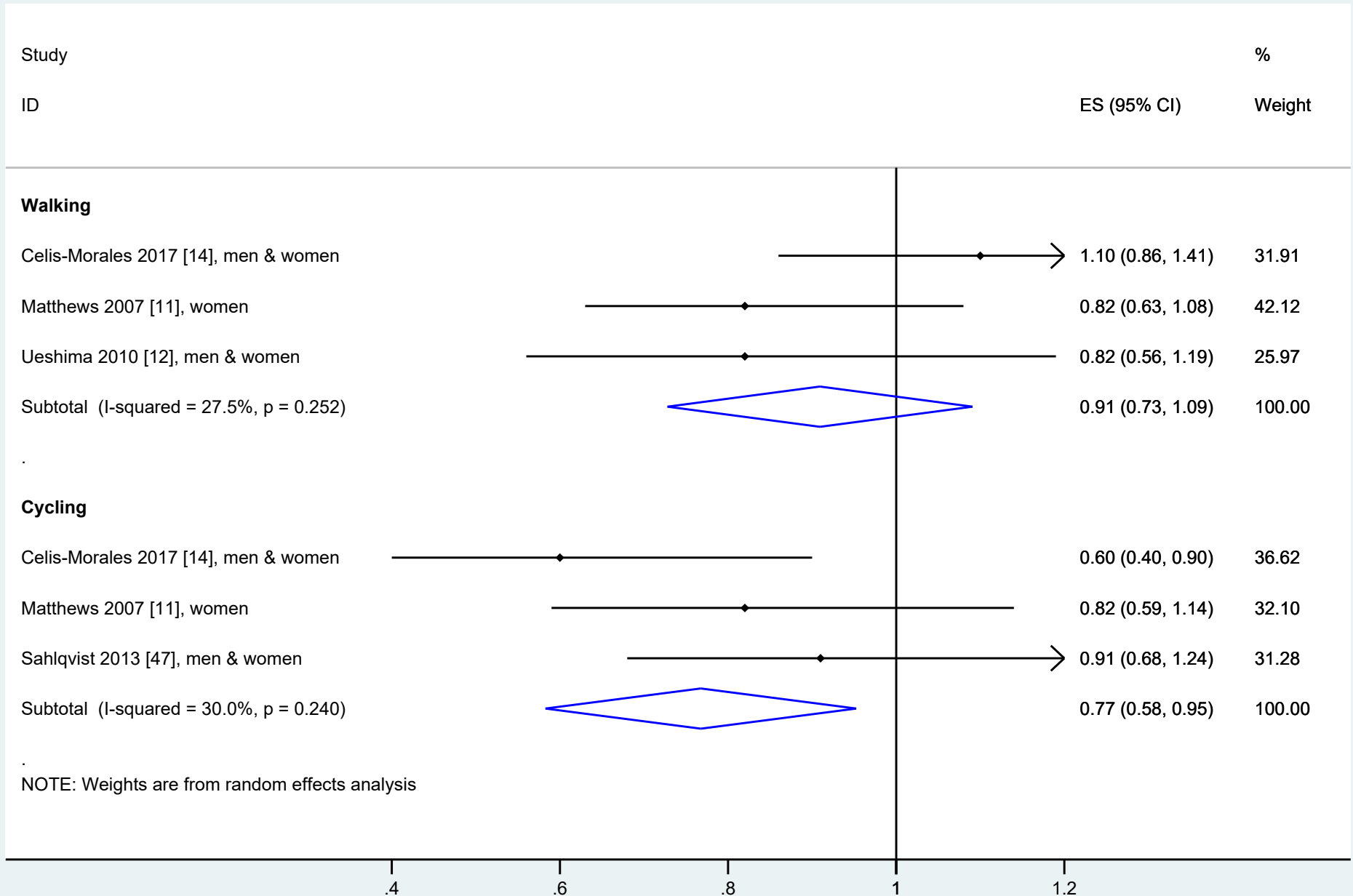
Benefits of active commuting on cardiovascular mortality

Stratified by type of active commuting - Crude or less adjusted hazard ratio



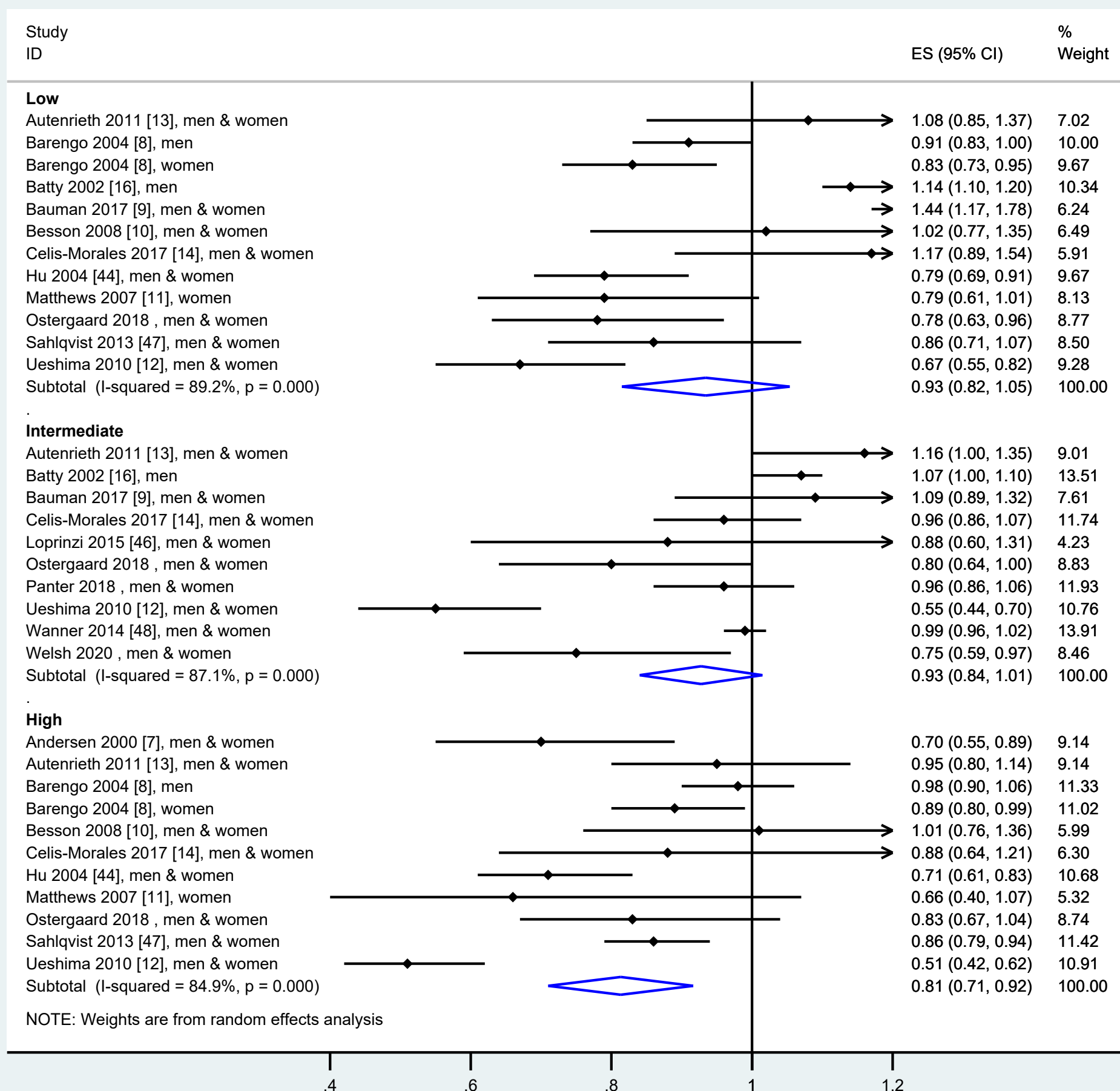
Benefits of active commuting on Cancer mortality

Stratified by type of active commuting - Crude or less adjusted hazard ratio



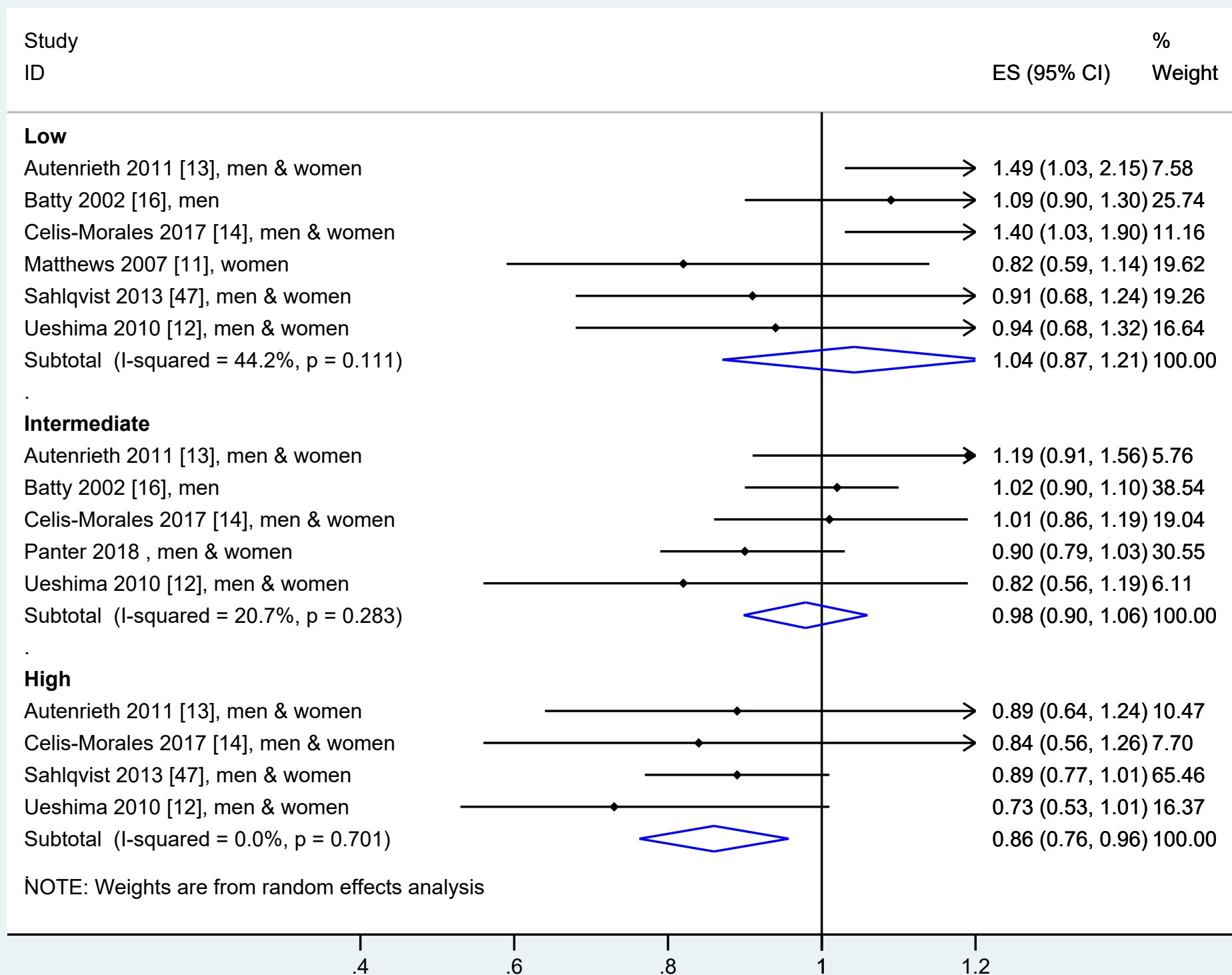
Benefits of active commuting on all-cause mortality

Stratified by level of active commuting - Crude or less adjusted hazard ratio



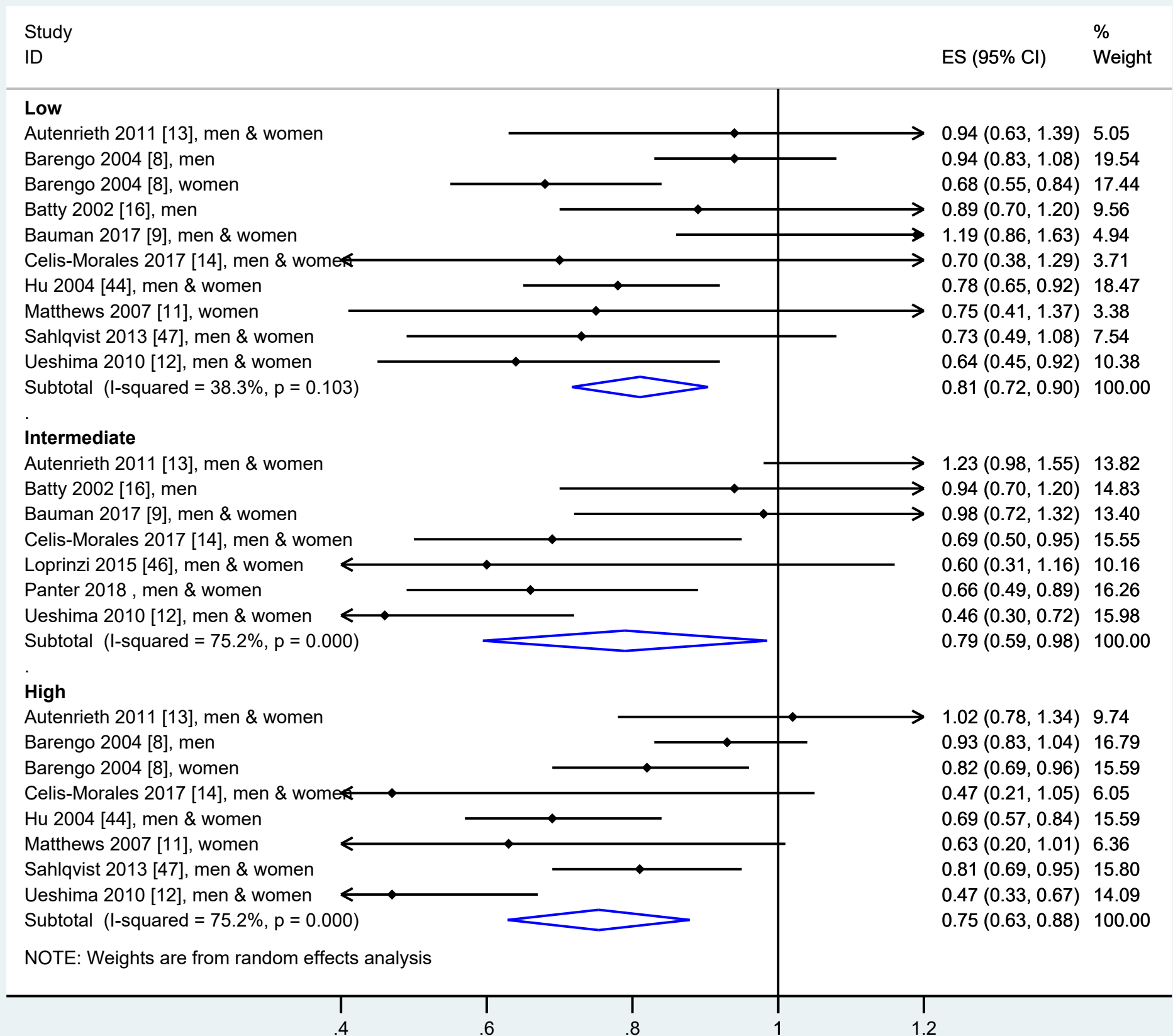
Benefits of active commuting on Cancer mortality

Stratified by level of active commuting - Crude or less adjusted hazard ratio

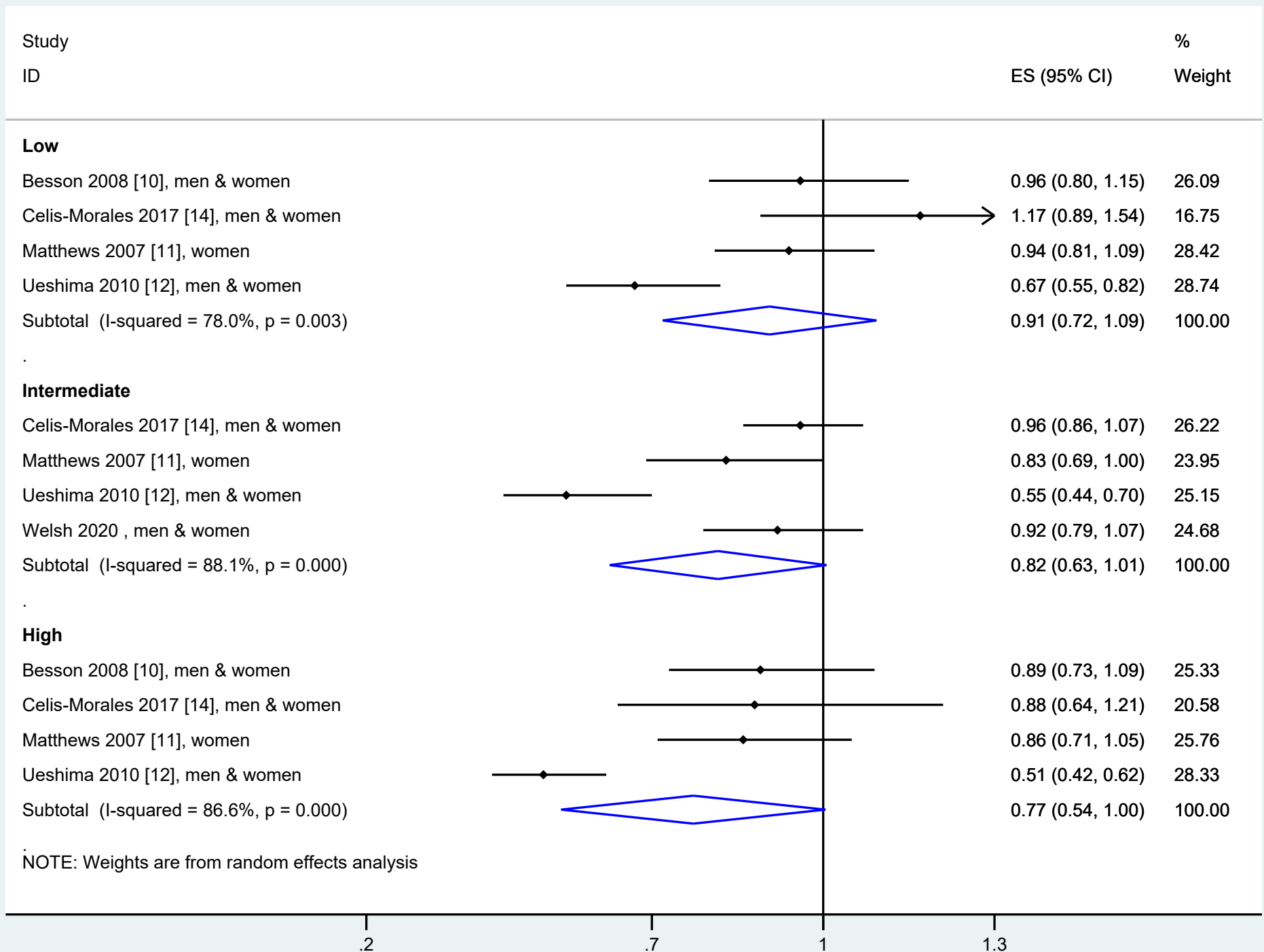


Benefits of active commuting on cardiovascular mortality

Stratified by level of active commuting - Crude or less adjusted hazard ratio

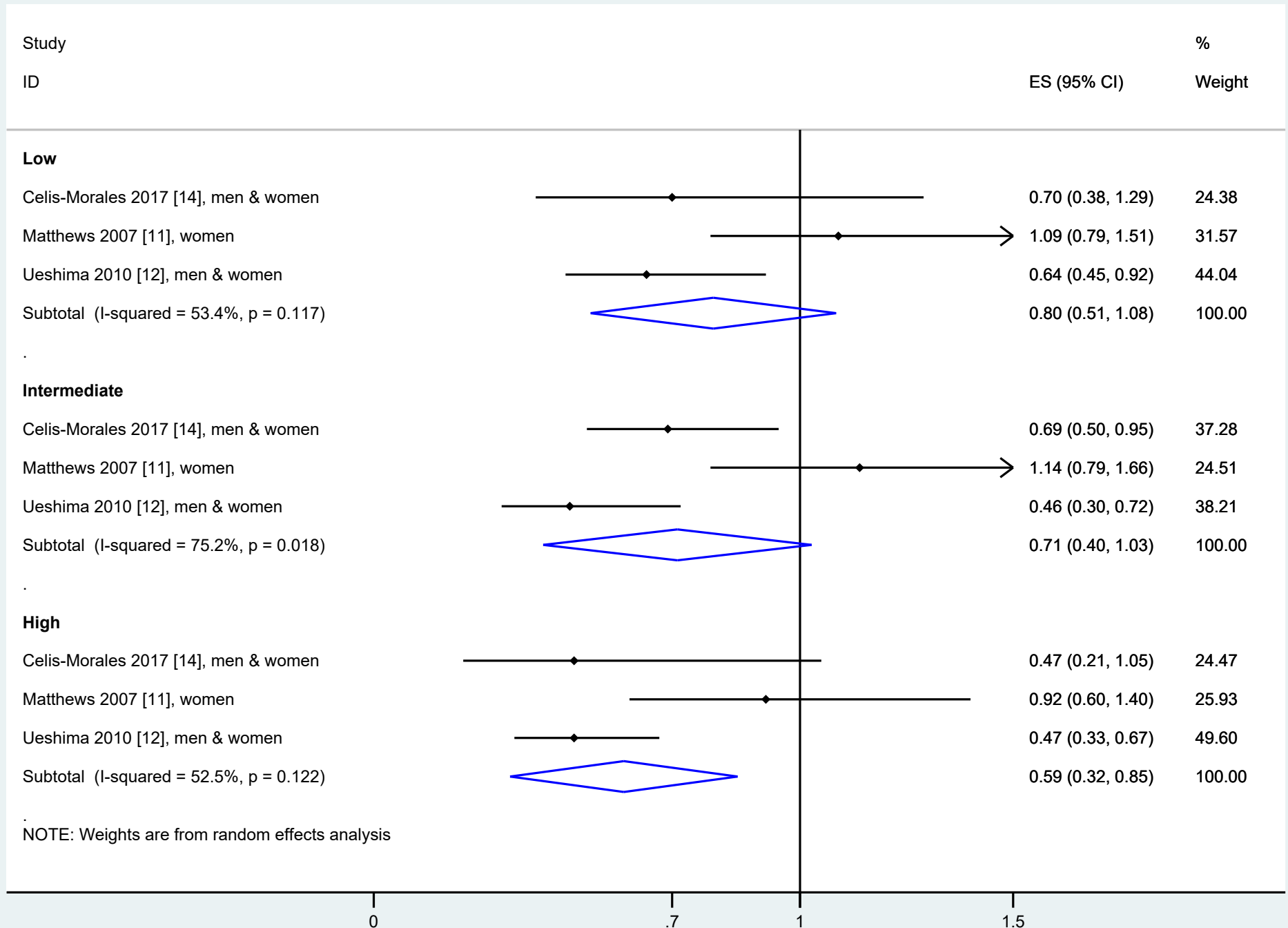


Benefits of active commuting by walking on all-cause mortality - Crude or less adjusted hazard ratio

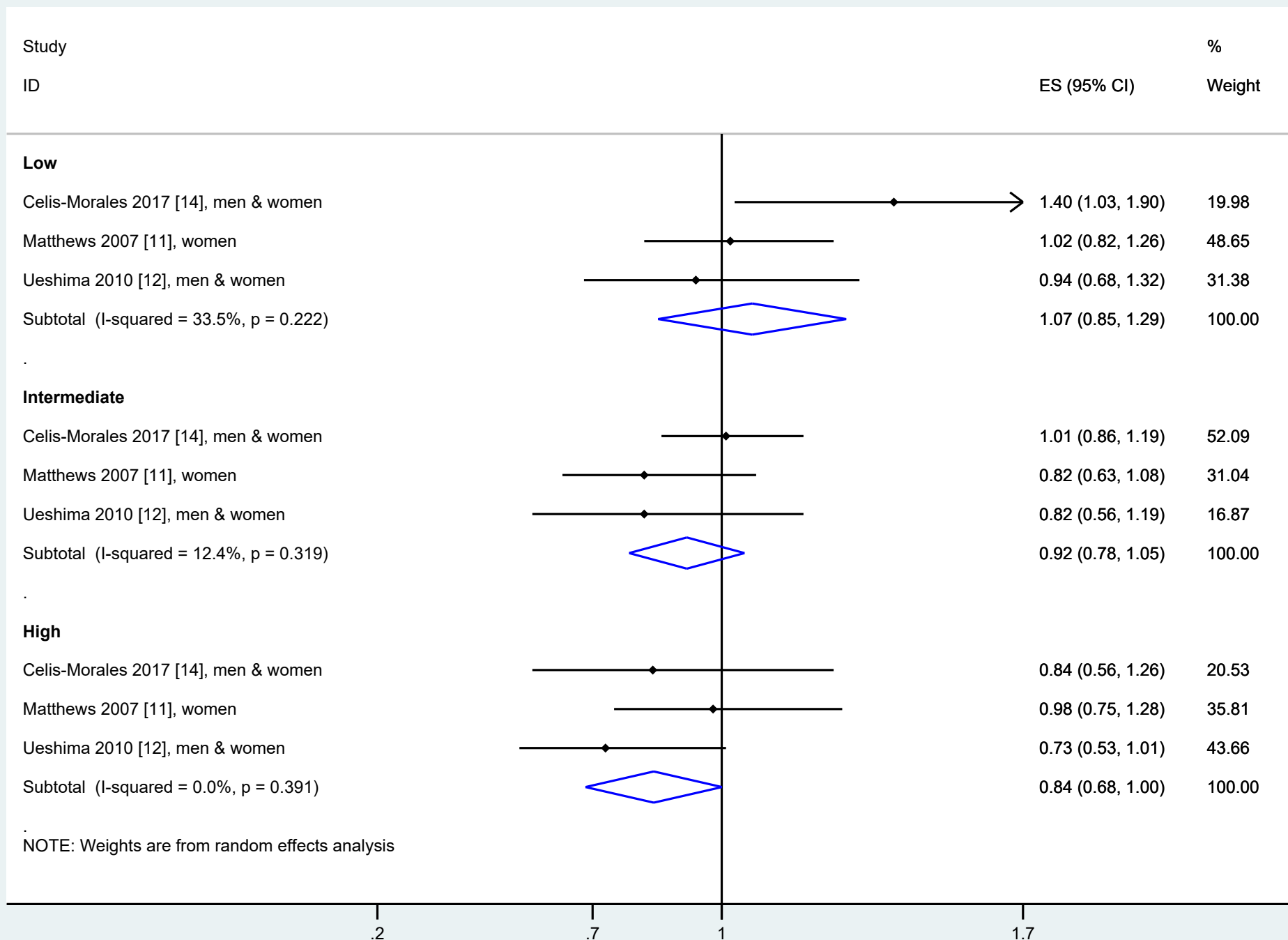


Benefits of active commuting by walking

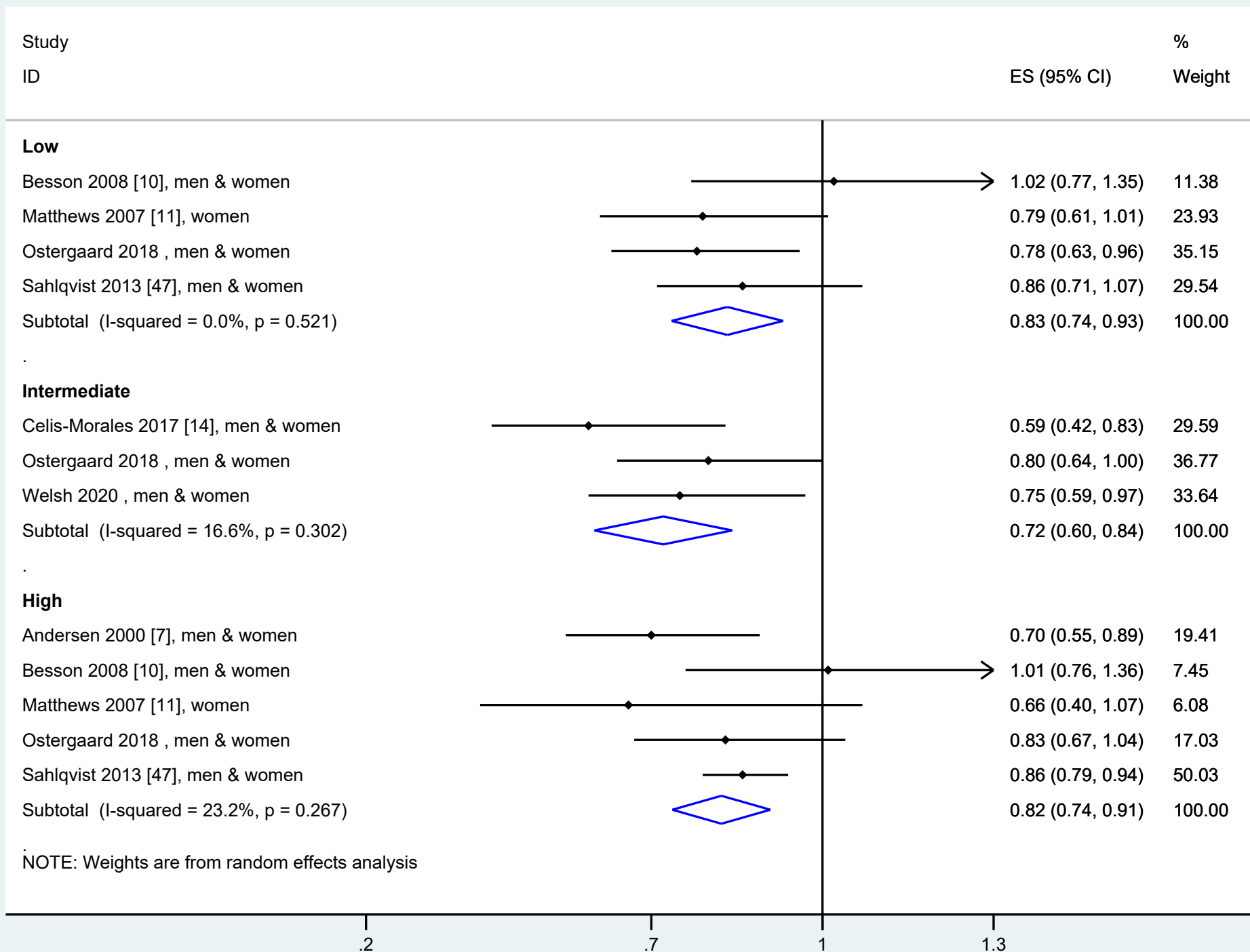
on cardiovascular mortality - Crude or less adjusted hazard ratio



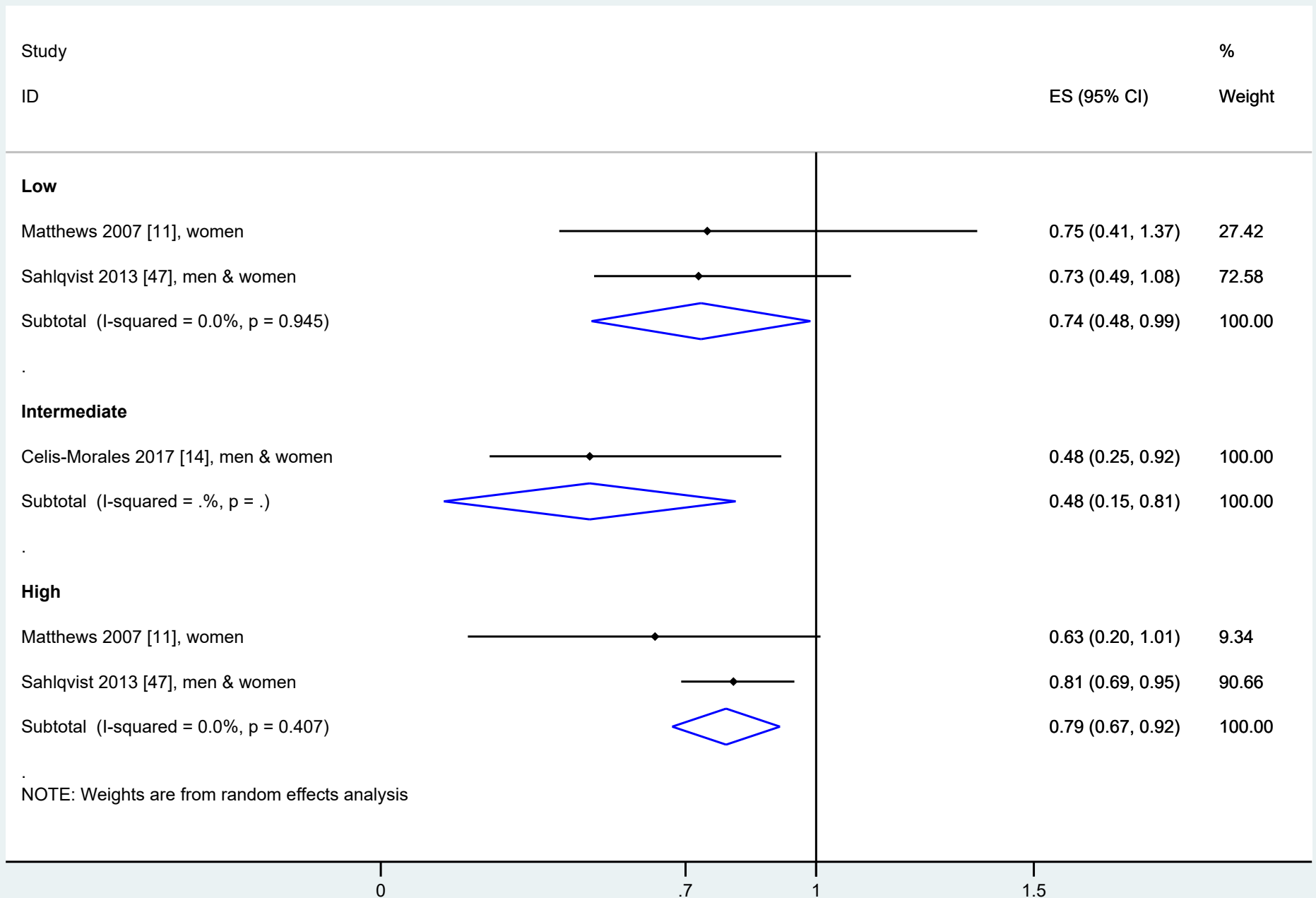
Benefits of active commuting by walking on cancer mortality - Crude or less adjusted hazard ratio



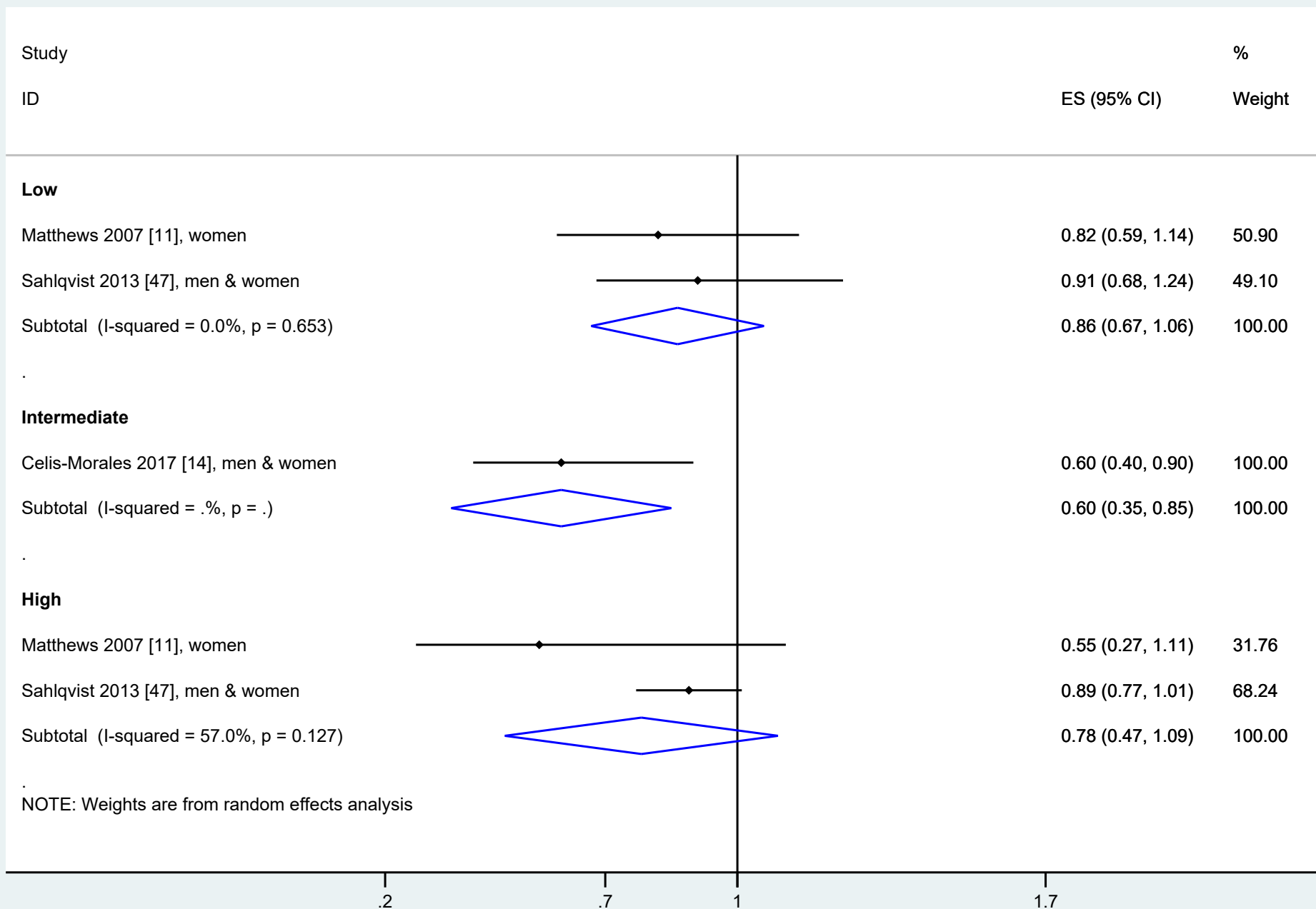
Benefits of active commuting by cycling on all-cause mortality - Crude or less adjusted hazard ratio



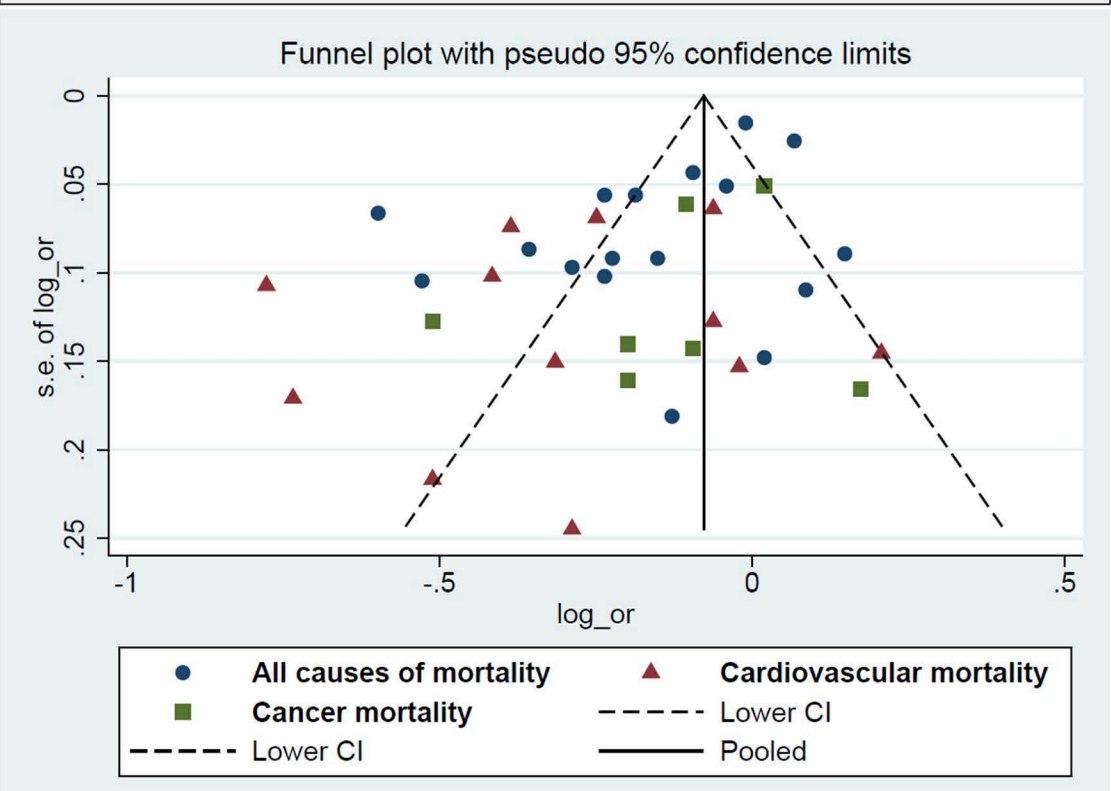
Benefits of active commuting by cycling on cardiovascular mortality - Crude or less adjusted hazard ratio odds ratio



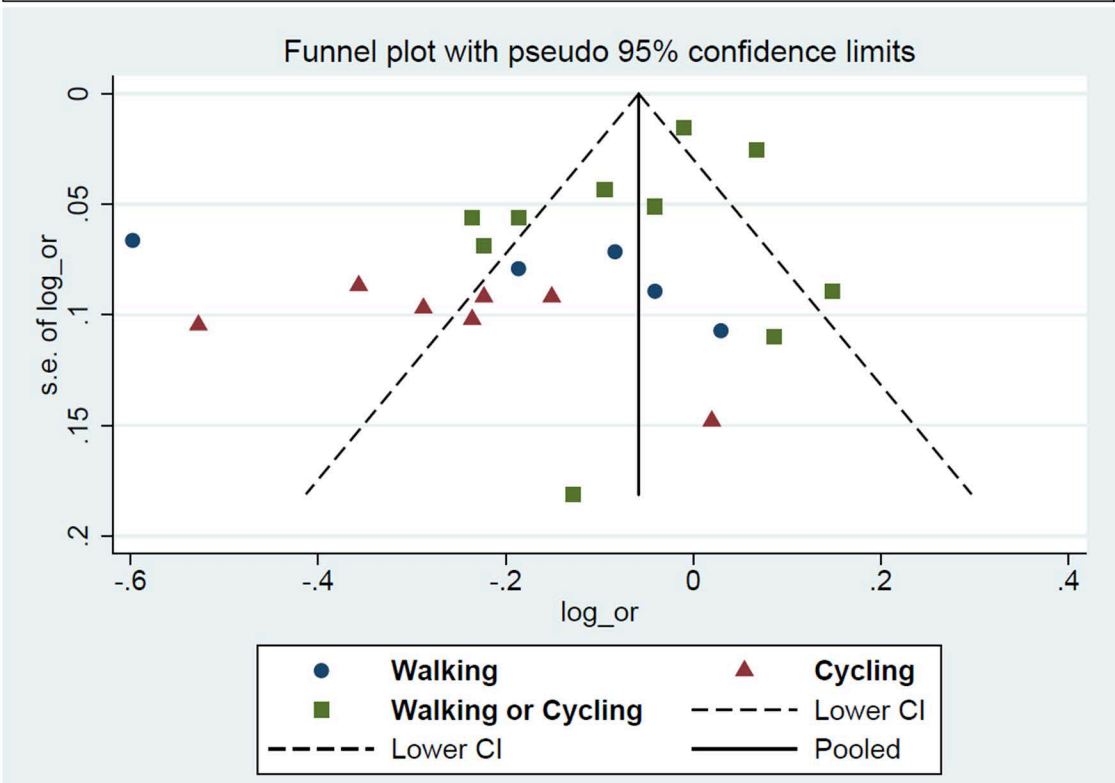
Benefits of active commuting by cycling on cancer mortality - Crude or less adjusted hazard ratio



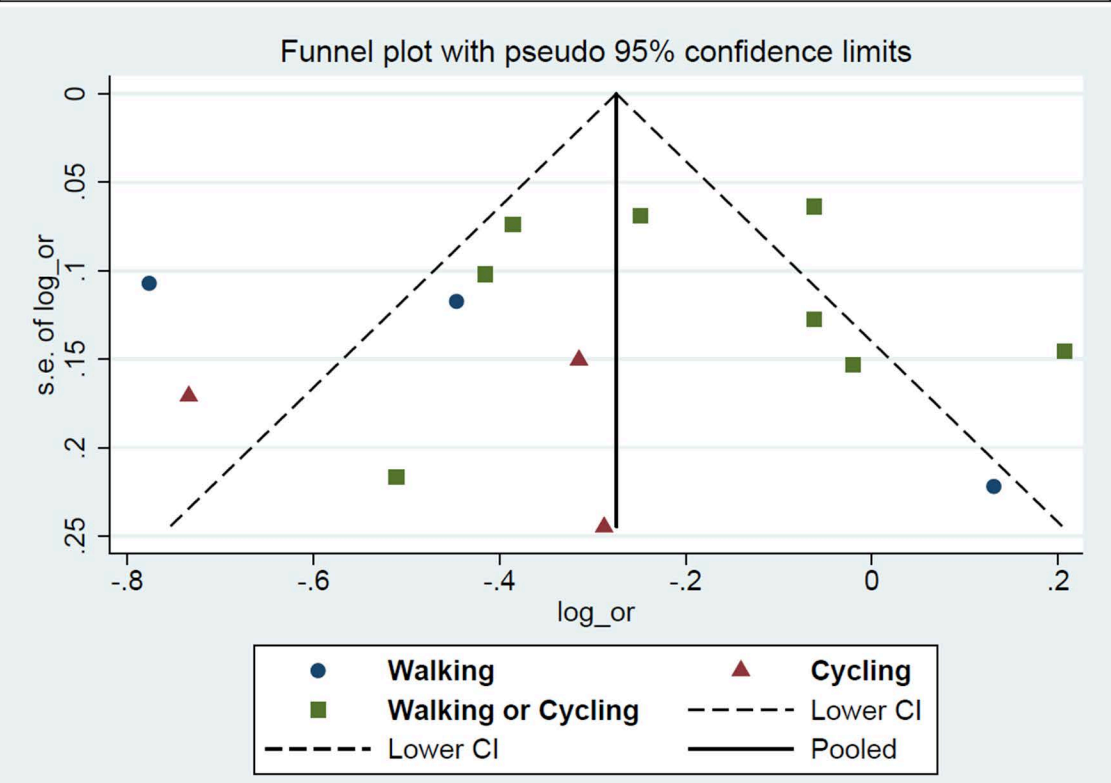
Benefits of active commuting by type of mortality (all cause, cardiovascular and cancer mortality) - Crude or less adjusted Hazard Ratio



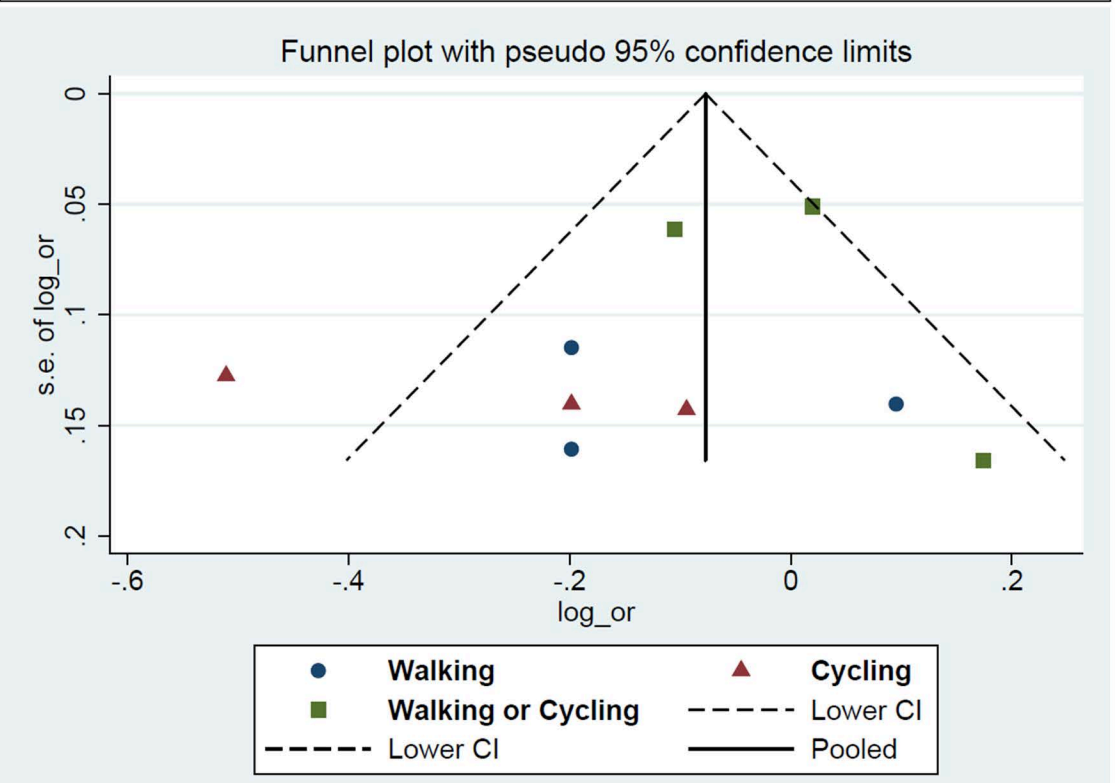
Benefits of active commuting on all-cause mortality stratified by type of commuting – Crude or less adjusted Hazard Ratio



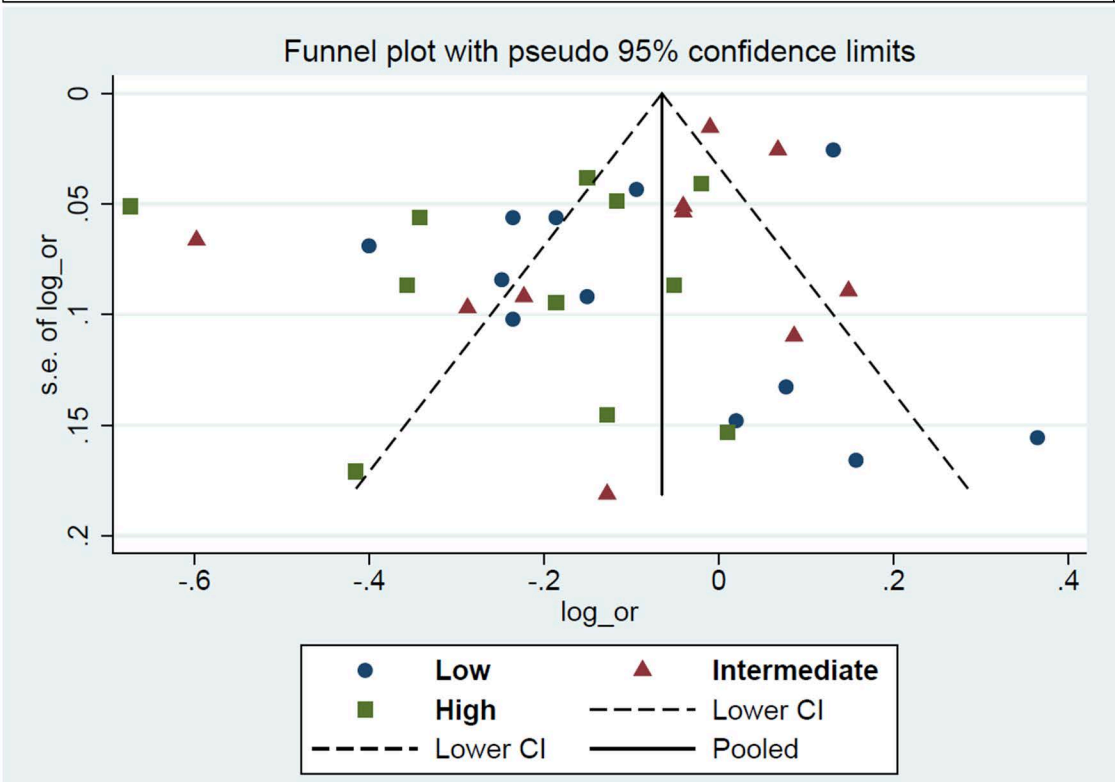
Benefits of active commuting on cardiovascular mortality stratified by type of commuting – Crude or less adjusted Hazard Ratio



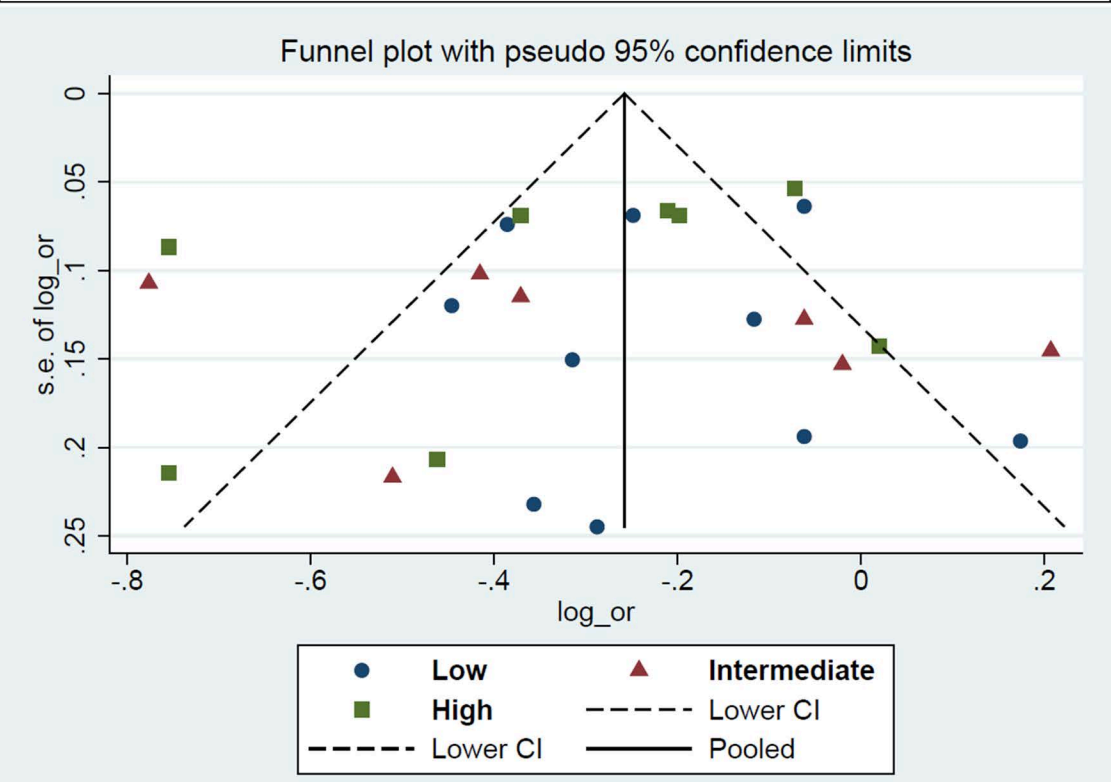
Benefits of active commuting on cancer mortality stratified by type of commuting – Crude or less adjusted Hazard Ratio



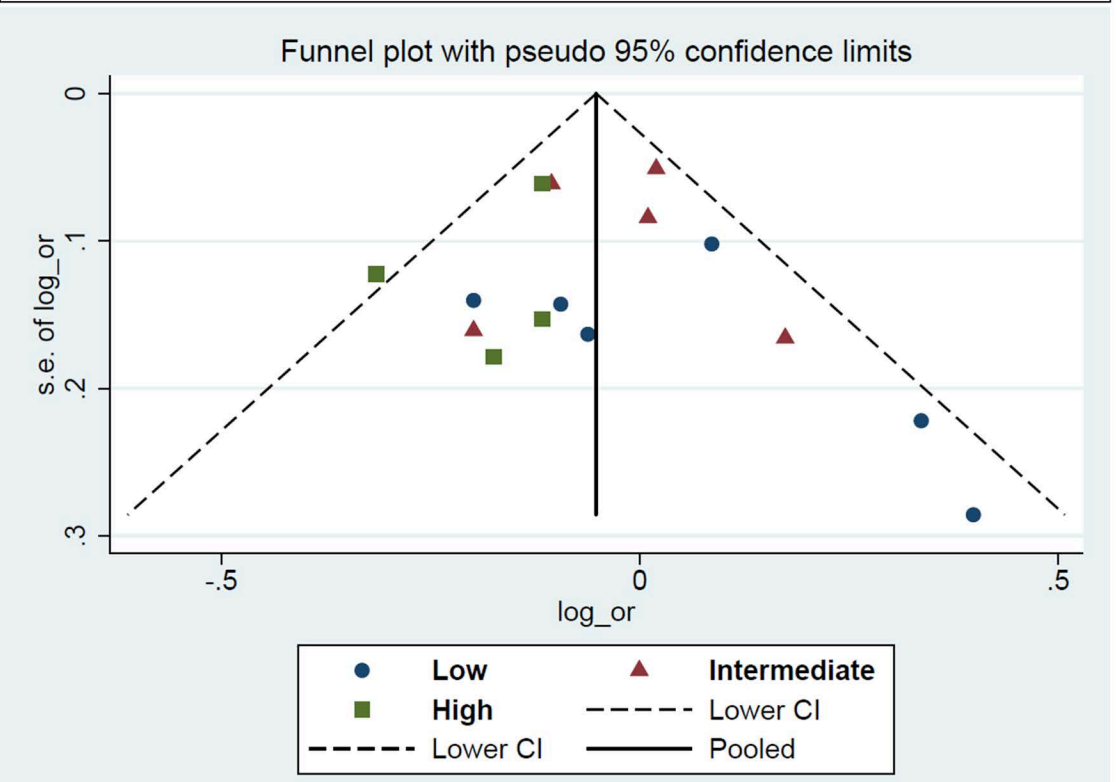
Benefits of active commuting on all-cause mortality stratified by level of active commuting – Crude or less adjusted Hazard Ratio



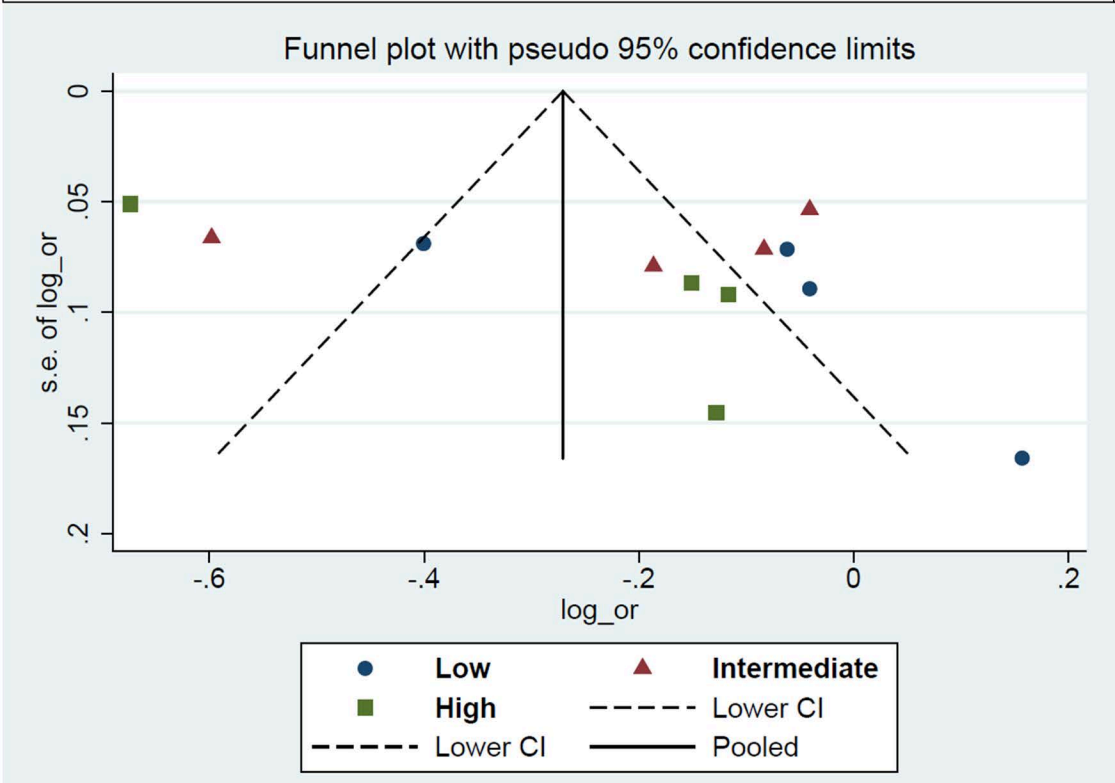
Benefits of active commuting on cardiovascular mortality stratified by level of active commuting – Crude or less adjusted Hazard Ratio



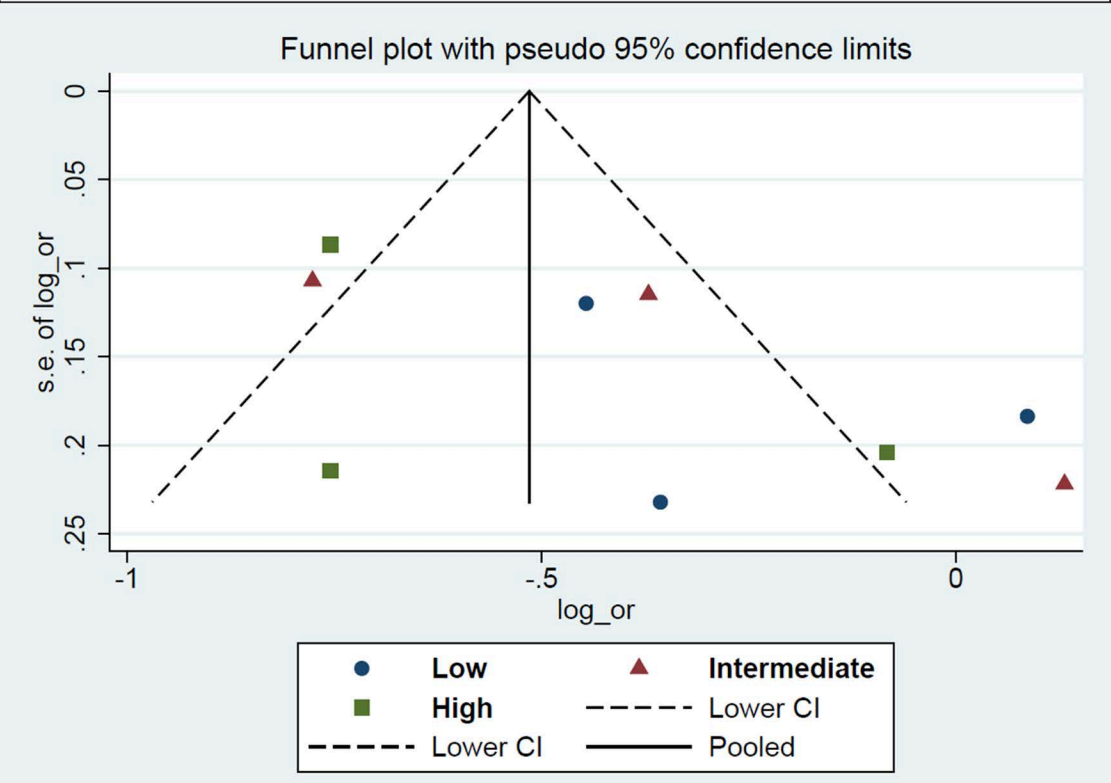
Benefits of active commuting on cancer mortality stratified by level of active commuting – Crude or less adjusted Hazard Ratio



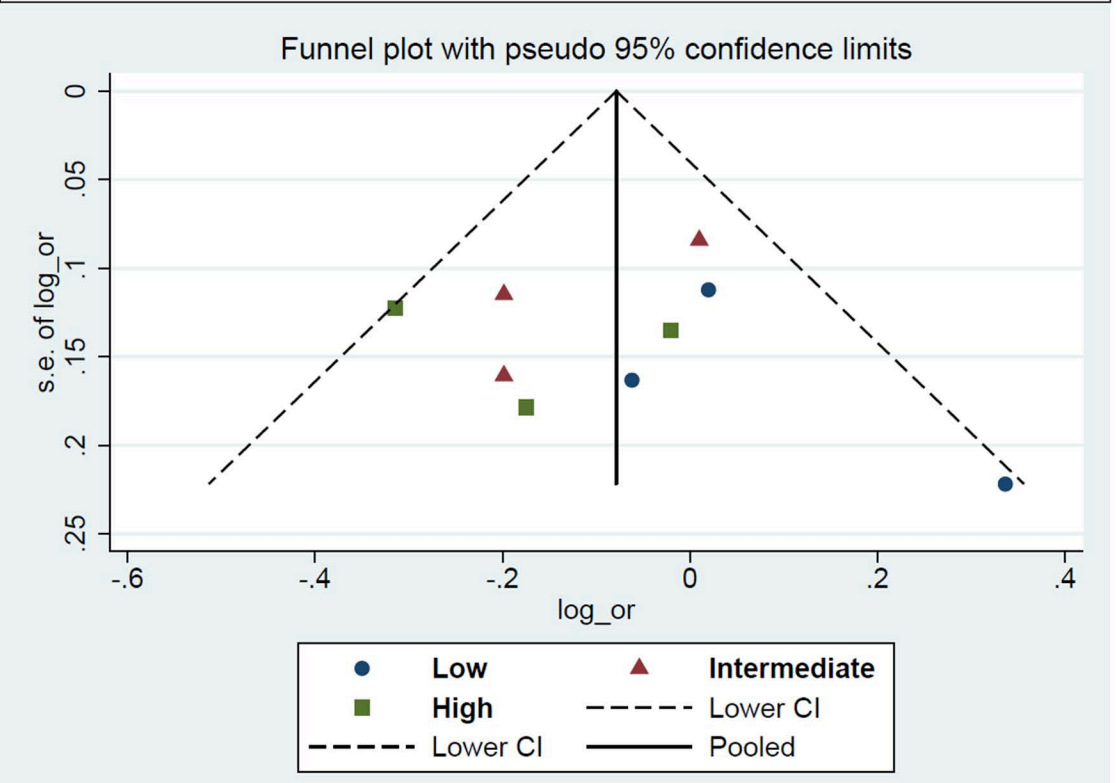
Benefits of active commuting by walking on all-cause mortality – Crude or less adjusted Hazard Ratio



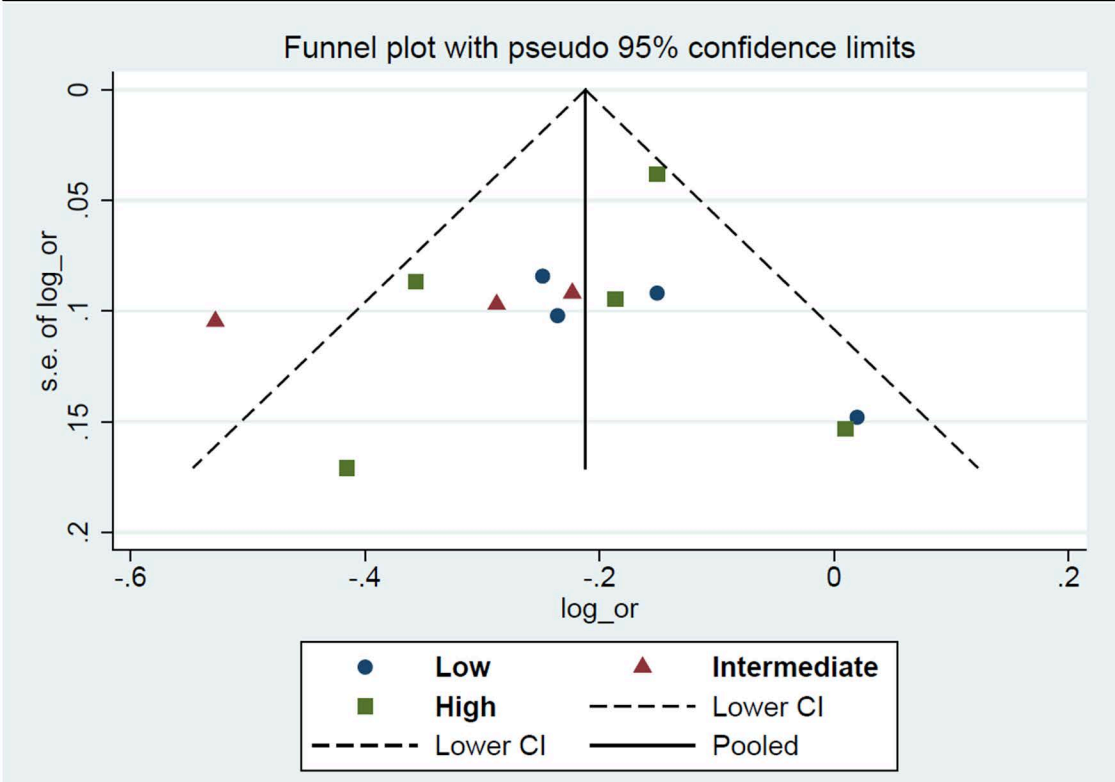
Benefits of active commuting by walking on cardiovascular mortality – Crude or less adjusted Hazard Ratio



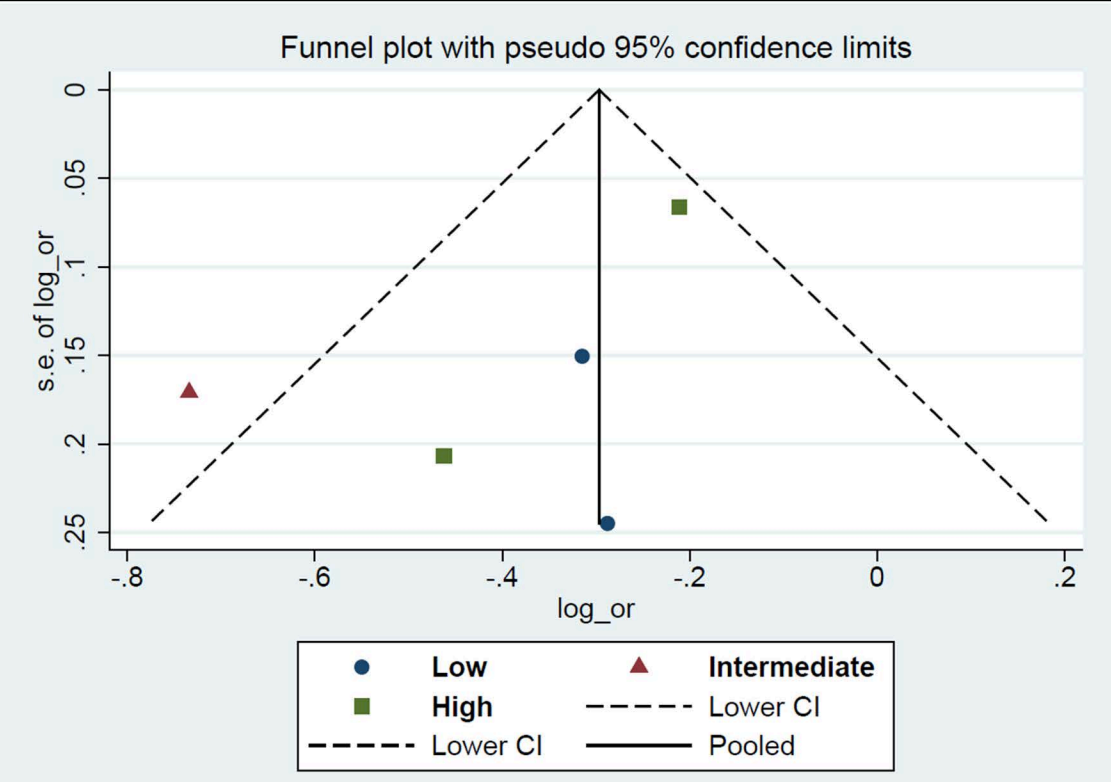
Benefits of active commuting by walking on cancer mortality – Crude or less adjusted Hazard Ratio



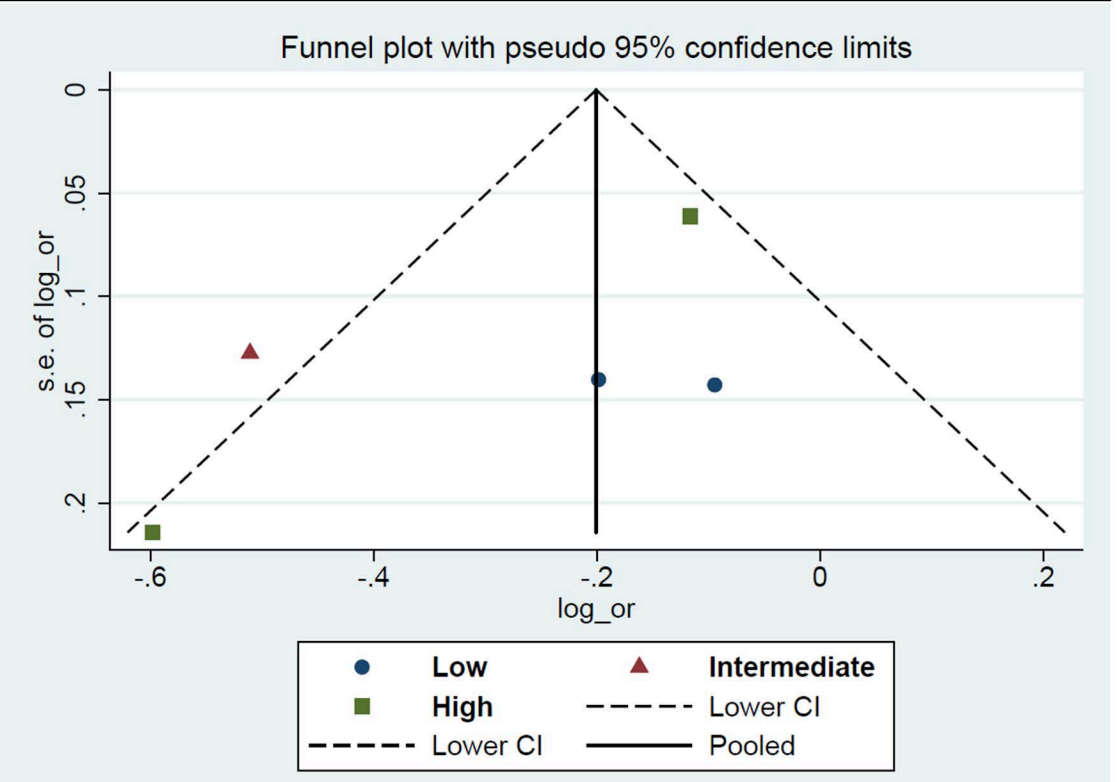
Benefits of active commuting by cycling on all-cause mortality – Crude or less adjusted Hazard Ratio



Benefits of active commuting by cycling on cardiovascular mortality – Crude or less adjusted Hazard Ratio



Benefits of active commuting by cycling on cancer mortality – Crude or less adjusted Hazard Ratio



Electronic Supplementary Material Appendix S1.

Details for the search strategy used within each database.

PubMed

(commuting OR commute)

AND

mortality

NOT (animals [MH])

NOT (child [Title] OR childs [Title] OR children [Title] OR Offspring [Title] OR minor [Title] OR adolescent [Title] OR adolescents [Title] OR teens [Title] OR teenagers [Title] OR teenager [Title] OR adolescence [Title] OR teen [Title])

Filter Language = none

Filter Dates = none

CENTRAL

commuting:*ti,ab,kw* OR commute:*ti,ab,kw*

AND

mortality:*ti,ab,kw*

NOT

child:*ti* OR childs:*ti* OR children:*ti* OR Offspring:*ti* OR minor:*ti* OR adolescent:*ti* OR adolescents:*ti* OR teens:*ti* OR teenagers:*ti* OR teenager:*ti* OR adolescence:*ti* OR teen:*ti*

Filter Language = not available in CENTRAL

Filter Dates = none

Web of science (WOS)

TS=(commuting OR commute)

AND

TI=(mortality)

NOT

TI=(child OR childs OR children OR Offspring OR minor OR adolescent OR adolescents OR teens OR teenagers OR teenager OR adolescence OR teen)

Filter Language = none

Filter Dates = none

Databased restricted to:

Science Citation Index Expanded (SCI-EXPANDED)

Conference Proceedings Citation Index- Science (CPCI-S)

Book Citation Index– Science (BKCI-S)

Emerging Sources Citation Index (ESCI)

Embase

(commuting OR commute)

AND

mortality

Electronic Supplementary Material Appendix S2. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6 and Fig1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6 and Fig1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6 and Fig1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6 and Fig1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6 and Fig1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6 and Fig1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6 and Fig2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-8

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6 and Fig2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-12 and Fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-12 and Fig + SFig
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-10 and Fig2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14 and Fig + SFig
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14 and Fig + SFig
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-10 and Fig2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14 and Fig + SFig
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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