General estimates of the energy cost of walking in people with different levels and causes of lower limb amputation: a systematic review and meta-analysis

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Abstract

Background: Energy cost of walking (ECw) is an important determinant of walking ability in people with a lower limb amputation. Large variety in estimates of ECw has been reported, likely due to the heterogeneity of this population in terms of level and cause of amputation and walking speed.

Objectives: To assess (1) differences in ECw between people with and without a lower limb amputation, and between people with different levels and causes of amputation, and (2) the association between ECw and walking speed.

Study Design: Systematic review and meta-analysis.

Methods: We included studies that compared ECw in people with and without a lower limb amputation. A meta-analysis was done to compare ECw between both groups, and between different levels and causes of amputation. A second analysis investigated the association between self-selected walking speed and ECw in people with an amputation.

Results: Out of 526 identified articles, 25 were included in the meta-analysis and an additional 30 in the walking speed analysis. Overall, people with a lower limb amputation have significantly higher ECw compared to people without an amputation. People with vascular transfemoral amputations showed the greatest difference (+102%) in ECw. The smallest difference (+12%) was found for people with non-vascular transtibial amputations. Slower self-selected walking speed was associated with substantial increases in ECw.

Conclusion: This study provides general estimates on the ECw in people with a lower limb amputation, quantifying the differences as a function of level and cause of amputation, as well as the relationship with walking speed.

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Key words: energy cost of walking, lower limb amputation, prosthesis, aetiology, level, walking speed

Background

In the Netherlands, the incidence of lower limb amputations is 20 per 100,000 population.[1] Each year, about 3,200 lower limb amputations are performed.[2] The group of people with a lower limb amputation is heterogeneous, including persons with different levels and causes of amputation and concomitant factors. This heterogeneity is considered a main contributor to differences in the level of functioning between persons with a lower limb amputation.[3] Level of amputation can be roughly divided into amputations below and above the knee, with transtibial and transfemoral amputations being the most common. The etiology of amputation can be roughly divided into vascular causes and non-vascular causes. Generally, lower limb amputations with a vascular cause are performed in older persons with medical comorbidities including diabetes, whereas lower limb amputations due to non-vascular causes often include younger persons with fewer comorbidities.[4] It has been established that both level and cause of amputation have a major effect on walking ability in people with a lower limb amputation.[3, 5-7]

Walking ability in people with a lower limb amputation is often assessed in terms of energy cost of walking (ECw). ECw has shown to be related to quality of life and participation in social activities.[8] It has frequently been found that people with a lower limb amputation have increased ECw compared to persons without an amputation.[6] After undergoing lower limb amputation, one can choose to walk with or without use of a prosthesis, which will both increase the ECw.[6] Walking without a prosthesis results in the highest ECw, as additional energy is needed to support body weight on crutches. Walking with a prosthesis also results in greater ECw, as the economy of gait is constrained by the prosthesis. People walking with a prosthesis show reduced ankle push-off power resulting from a reduced ability to plantar flex their ankle. Consequently, people with a lower limb amputation need to use other, less efficient, strategies for propulsion and leg swing.[9-11] Impaired balance control is considered another factor contributing to increased ECw while walking with a prosthesis.[7, 12] People with a lower limb prosthesis are known to be less stable during steady-state walking compared to people without an amputation.[12, 13] This requires the use of compensatory strategies in order to maintain balance, resulting in increased energy demands.[12, 14-16]

Over the last fifty years, many studies have investigated the ECw in people with a lower limb amputation. The seminal study of Waters et al.[6] was one of the first studies to systematically investigate the ECw for people with different levels and causes of amputation. Results showed that the ECw in people with a lower limb amputation is dependent on both level and cause of amputation. They reported increases of 25% and 55% in ECw, for persons with a non-vascular amputation at the transtibial and transfemoral level respectively, compared to persons without an amputation. For persons with a vascular amputation, the reported values were even higher, with increases of 65% and 120% for persons with a transtibial and transfemoral amputation respectively. These values as reported by Waters et al.[6] - and re-evaluated in a later review[17] - are still often used as reference values in clinical practice, since the study of Waters et al. is actually the only study that systematically compared ECw in subgroups stratified for all levels and causes of amputation within one study. However, it can be questioned whether the values provided by Waters et al.[6, 17] are applicable to the current population of people with a lower limb amputation, as the sample size in the study was rather small (approximately 15 persons for each subgroup of people with an amputation and 5 people without an amputation) to generalize results to the whole population of persons with a lower limb amputation, which might limit precision of the provided estimates. Moreover, patient characteristics, prosthetic developments and assessment methods may have changed over time. .,

In the years following the seminal research of Waters et al.[6], the ECw for people with a lower limb amputation has been assessed in many other studies.[9, 18-20] However, these studies have predominantly focused on one specific cause or level of amputation.[9, 18-20] In addition, a great variety of types of prostheses has been analysed, as ECw has often been used as an outcome to test a newly developed prosthesis.[21, 22] Few of these studies included a control group of people without an amputation. Moreover, studies differ in their experimental protocol, using different walking speeds and walking surfaces.[23, 24] Walking speed has been shown to substantially influence ECw, both in people with and without lower limb amputation.[25] ECw is known to have a U-shaped relation with walking speed, increasing at both slow and fast walking speeds.[25] It has been shown that, in contrast to persons without an amputation, people with a lower limb amputation walk at speeds slower than their most economic speed.[26] Therefore differences in self-selected walking speed can be associated with differences between individuals and subgroups. This can be controlled by studies that use a fixed imposed walking speed rather than self-selected walking speed in order to assess the ECw. However, these ECw outcomes are not representative for walking in daily life.

Hence, despite the availability of a large (and still growing) amount of quantitative data on the ECw with a lower limb prosthesis, general estimates on the magnitude of the difference in energy cost relative to walking in persons without a lower limb amputation are difficult to derive from the available data due to the heterogeneity between study populations and designs. Still, clinical practice and prosthetic developments need such information in order to set patient-specific expectations for ECw and to develop benchmarks and interventions to reduce the ECw. Therefore, the purpose of this study is to compare the ECw between people with and without a lower limb amputation, and to assess to what extent ECw differs as a function of level and cause of amputation. In addition, we investigated the association between self-selected walking speed and ECw of people with a lower limb amputation, in order to assess how self-selected walking speed might account for the variation in energy cost between and within subgroups.

Methods

Search strategy

We performed an electronic search via the following databases until March 2020: PubMed, Physiotherapy Evidence Database (PEDro) and Cumulative Index to Nursing and Allied Health Literature (CINAHL). A detailed description of the applied search strategy is provided in Appendix 1. Searches were pre-limited using the following criteria: English language and abstract available. Articles were further selected by reading title and abstract, after which a final selection was made based on the full article. Articles were selected for two types of analysis. In *analysis 1*, we compared the ECw between people with a lower limb amputation, stratified for level (transtibial vs. transfemoral) and cause (vascular vs. non-vascular) of amputation, and persons without an amputation. In *analysis 2*, we assessed the effect of self-selected walking speed on ECw. Articles selected for *analysis 2* did not need to include people without an amputation. All included articles needed to provide explicit data concerning average and standard deviation of ECw and walking speed and meet all other inclusion criteria described below. When an article had been selected for either *analysis 1* or *analysis 2*, but did not provide all required details, the author was approached to provide the exact data. One author (XX) selected articles and extracted data. Another author (YY), checked the selection and data extraction of all articles. If discrepancies existed, the authors conferred to reach consensus on the specific issue.

Inclusion criteria

The following inclusion criteria were used when selecting studies: *1)* participants are at least 18 years of age; *2)* inclusion of a control group without amputation (*analysis 1* only); *3)* inclusion of participants with transtibial or transfemoral amputation; *4)* measurement of energy consumption during walking (for people with an amputation: during walking with prosthesis); *5)* energy consumption measured by indirect calorimetry; *6)* the article is not a case-study or a review article.

Data extraction, outcome measures and risk of bias assessment

The following information was extracted from the selected articles: *1)* subject characteristics (e.g., age, gender); *2)* level of amputation; *3)* cause of amputation; *4)* system used for measuring oxygen consumption and calculation of the ECw; *5)* type of prosthetic component used; *6)* study design (instructions, duration and environment); *7)* ECw; *8)* walking speed at which ECw was assessed.

When an article investigated the ECw for a group of people with mixed levels and/or causes of amputation, the author was approached to provide additional information needed to subgroup persons according to the level and cause of amputation. Subgroups with fewer than three participants were excluded from further analysis. When a particular study tested multiple types of prostheses in the same group of participants, the ECw and walking speed related to the prosthesis with the most widespread clinical use at the time of the study were used for further analysis (see Appendix 2 for detailed selection, not chosen options are provided in italics). The prosthesis with most widespread clinical use was selected by one author with longstanding experience in the field (YY). In the case that ECw had been assessed during both overground and treadmill walking, we used the ECw during overground walking for further analysis, as this most closely resembles walking in daily life.[27] For each study, one combination of walking speed and ECw was used for analysis. If ECw had been assessed both at imposed and self-selected walking speeds, we used ECw values at self-selected walking speed for further analysis. Furthermore, when ECw had been measured only at multiple imposed walking speeds, we selected the ECw associated with the walking speed that was closest to the average self-selected walking speed of the specific subgroup. Average self-selected walking speed for each specific subgroup was based on the preferred walking speed found in other selected studies: transfemoral vascular: 0.52 $m\ s^{-1}$; transfemoral non-vascular: 1.00 $m\ s^{-1}$; transtibial vascular: 0.79 $m\ s^{-1}$; transtibial non-vascular: 1.34 $m\ s^{-1}$. Summary information regarding study protocols of included studies is presented in Appendix 3.

Two of the reviewers (XX, ZZ) independently assessed the risk of bias of the included studies with the Newcastle-Ottawa Scale (NOS[28]), which was modified for the study purpose (see Appendix 4). The NOS contains items on participant selection, comparability of the study groups and outcome assessment. The scale ranges from 0-11 for *analysis 1* and from 0-7 for *analysis 2*, as comparability items were not relevant for *analysis 2*. Higher NOS-scores reflect a lower risk of bias.

Energy cost calculations

In this study, we analysed the gross metabolic ECw expressed in ml O_2 kg^{-1} m^{-1}. When studies only reported oxygen consumption ($\dot{V}O_2$; ml O_2 kg^{-1} min^{-1}), ECw was calculated by dividing oxygen consumption by walking speed (in m min^{-1}). When actual metabolic energy expenditure ($\dot{E}E$) was provided in J kg^{-1} s^{-1} it was converted into ml O_2 kg^{-1} m^{-1} according to Equation (1), with walking speed (*v)* expressed in m min^{-1}. Respiratory exchange ratio (RER) was assumed to be equal to 1.[29]

$$ECw = \frac{\dot{E}E \ \times 60 \ \times v}{(4.940 \ \times RER + 16.040)} \qquad (1)$$

Meta-analysis calculations

In order to perform a meta-analysis with the data collected for *analysis 1*, the standard deviation (SD) of ECw was needed. When articles did not report SD, 95% confidence interval was used to determine SD, according to Equation (2). Studies to which Equation (2) was applied are indicated with an asterisk (*) in Appendix 2. When articles did not report SD nor 95% CI and when this data could not be retrieved from the original author, articles were excluded from *analysis 1*.

$$SD = \frac{\sqrt{N} \times (upper\ limit\ 95\%\ CI - lower\ limit\ 95\%\ CI)}{3.92} \qquad (2)$$

Meta-analysis

Meta-analyses were carried out with RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Since all included studies used the same outcome measure with similar (or converted to similar) units of measurement, data were pooled using the mean difference (MD). Significance level was set at $p<0.05$. Random effects models were used (as a high level of heterogeneity was evident, and > 5 studies were available). Statistical heterogeneity was confirmed by visual inspection of the forest plots, and with the I^2-statistic, with heterogeneity considered to be present if χ^2 was significant ($p<0.1$).[30] We sub grouped studies according to the level (transtibial vs. transfemoral) and cause (vascular vs. non-vascular) of amputation, to assess if ECw would be different for people with different combinations of levels and causes of amputation. When an article provided data for different subgroups of persons (i.e. different levels/causes of amputation) but for just one single control group, the means and SDs for this particular control group were used as many times in the same analysis, but we divided the sample size by the number of comparisons it was included in.[30]

Analysis of walking speed

The relationship between walking speed and ECw was analysed descriptively by fitting a polynomial through the available data of ECw and self-selected walking speed of different subgroups. The curves were second-order polynomial fits through all data points of a specific subgroup, which were described by the function: $ECw = av^2 + bv + c$. Walking speed was expressed in m s^{-1}. For each study, only one specific estimate of ECw (i.e. at actual or approximated self-selected walking speed) was added to this analysis. These analyses were performed in Matlab (The Mathworks, Natick, MA, USA) using the function *polyfit*.

Results

3.1 Literature search

Figure 1 shows the flow of study selection. In total, our search identified 526 articles. After screening of titles and abstracts, 40 potential articles were selected for *analysis 1* and 87 additional potential articles for *analysis 2*. Application of the in- and exclusion criteria eventually resulted in the inclusion of 35 articles in *analysis 1* and 41 additional articles in *analysis 2*. Most common reasons for exclusion at this stage were: unavailability of full text paper, measurement of energy consumption by other means than indirect calorimetry, and data for a group of persons that had already been presented in an earlier published article that was already included (see Figure 1). Regarding *analysis 1*, the results of 10 articles were only descriptively synthesised, but not included in the meta-analysis. Reasons for this were that the required data could not be extracted reliably and missing data could not be obtained by contacting the authors[31-36] (N=6), that standard deviations could not be obtained[20, 37] (N=2), outlying data (extremely high ECw values[38]; N=1), or analysis of ECw in the presence of external stimuli[39] (N=1; referred to as ‘other’ in Figure 1). In *analysis 2*, 11 articles were fully excluded from analysis, because no accurate data extraction was possible (N=11).

In sum, we selected 25 articles for the meta-analyses in *analysis 1* and 30 additional articles for the walking speed analysis in *analysis 2*.

[insert Figure 1]

3.2 Study characteristics

3.2.1 Participants characteristics

In total, 367 persons with a lower limb amputation and 282 persons without an amputation participated in the selected articles for *analysis 1* and 362 additional persons with a lower limb amputation participated in the selected articles for *analysis 2.* Table 1 shows the number and type of specific subgroups that were described in the included articles for analysis 1 and 2. Most of the included articles investigated persons with a non-vascular transtibial or transfemoral amputation. Considerable heterogeneity was noted in terms of participants’ characteristics, such as mean age (range controls: 23–60 years; range people with amputation; 22-73 years), gender (85% male), walking speed (range controls: 0.83–1.56 m s^{-1}; range people with amputation: 0.45–1.50 m

s^{-1}) and time since amputation (range: 9 weeks–31 years). For details for each of the studies, please see the overview tables in Appendix 2 and Appendix 3.

[insert Table 1]

3.2.2 Experimental protocol

In *analysis 1*, 18 articles assessed ECw using preferred walking speed, whereas 7 articles used an imposed fixed walking speed. Regarding walking surface, 12 articles performed their measurements on a treadmill and 13 articles performed overground measurements, either indoor or outdoor. In *analysis 2*, 20 articles studied ECw while walking at preferred walking speed, whereas 10 articles studied ECw at an imposed fixed speed. In *analysis 2*, 20 articles investigated ECw using a treadmill and 10 articles investigated ECw during overground walking. The duration of the walking trials varied between 2 and 20 minutes. All studies, except for two, did report the requirement of steady state walking. In both *analysis 1* and *analysis 2*, 14 studies used the average value over the last 2 or 3 minutes of their walking trials for analysis of the energy cost. Other studies took the average over shorter time periods, whereas 2 studies in *analysis 1* and 3 studies in *analysis 2*did not provide clear information about the use of averaging methods when calculating the energy cost.

3.3 Risk of bias assessment

Appendix 5 shows the NOS-scores of each study for *analysis 1 and 2*. Mean score and standard deviation were 6.4 ± 2.2 (range: 2-9) for *analysis 1*, and 4.5 ± 0.9 (range: 2-6) for *analysis 2*. For most studies, stars were awarded for clear descriptions of the study groups and the applied protocol. Overall, stars were often withheld for items relating to the selection and follow-up of study groups, as this was often not explicitly described. In *analysis 1,* comparability of the groups was often achieved in terms of age and sex of the participants, but only in a few studies were groups comparable in terms of physical fitness or physical activity levels.

3.4 Data analysis

3.4.1 Meta-analyses

A total of 25 studies (describing 37 comparisons) were included in the meta-analysis that investigated the difference in ECw between people with and without an amputation at self-selected walking speed. Results showed that persons without an amputation overall have significantly lower ECw compared to people with a lower limb amputation (MD=0.06 ml O_2 kg^{-1} m^{-1}, 95% CI=[0.04; 0.07], Z=8.80, p<0.001; see Figure 2).

Considerable heterogeneity was present (I^2=88%). Subgroup analyses revealed that the difference in ECw was significantly different as a function of levels and causes of amputation ($\chi^2(3)=165.92$, $p<.001$, I^2=98.2%). ECw was significantly higher compared to controls in all four subgroups (see Figure 2). The highest ECw was observed for people with a vascular transfemoral amputation (MD=0.18 ml O_2 kg^{-1} m^{-1}, 95% CI=[0.16, 0.21]), followed by the non-vascular transfemoral group (MD=0.07 ml O_2 kg^{-1} m^{-1}, 95% CI=[0.06, 0.08]), the vascular transtibial group (MD=0.06 ml O_2 kg^{-1} m^{-1}, 95% CI=[0.03, 0.09]), while the smallest (yet still significant) difference in ECw was observed for the non-vascular transtibial group (MD=0.02 ml O_2 kg^{-1} m^{-1}, 95% CI=[0.01, 0.03]). As can be seen in Table 2, the increase in ECw was significantly different between all subgroups ($p\leq.02$), except for the comparison of the non-vascular transfemoral group and vascular transtibial group (p=.58).

When expressed as a percentage of the weighted average of ECw of the respective control groups, the ECw for people with a lower limb amputation at self-selected walking speed was 35% higher compared to people without an amputation. When separately assessed for each of the subgroups, ECw values were 12% higher for the non-vascular transtibial group, 36% for the vascular transtibial group, 41% for the non-vascular transfemoral group, and 102% for the vascular transfemoral group.

[insert Figure 2]

[insert Table 2]

3.4.2 Descriptive synthesis

We descriptively synthesized the results of the 10 articles that were excluded from the meta-analysis, because no reliable data extraction was possible. All of the excluded articles investigated the ECw related to level of amputation, and did not directly compare groups with different causes. Most of the articles showed results that were similar to the results found in the meta-analysis. Do Nascimento Garcia et al.,[38] Herr and Grabowski,[36] Gailey et al.[20], Jaegers et al.[33], Schnall et al.[39], and Ladlow et al.[35] all showed significant increases in ECw for persons with a non-vascular amputation at the transtibial or transfemoral level compared to persons without an amputation, with the largest increase found for persons with a transfemoral amputation. This result was also found by Ganguli et al.,[32] but they did not report any significance values. Similar results were reported by Pinzur et al.,[37] in people with vascular transtibial and transfemoral amputations, but they did not report significance values either. The studies of Kark et al.[34] and Eckard et al.[31] seemed to deviate slightly from the results in the meta-analysis. Kark et al.[34] investigated ECw in transtibial amputees and transfemoral amputees with different causes of amputation, but only found significantly increased ECw for transfemoral amputees compared to people without an amputation. Eckard et al.[31] did not find any differences in ECw in a group consisting of both people with transtibial and transfemoral non-vascular amputations compared to persons without an amputation.

3.4.3 The relation between ECw and self-selected walking speed

Figure 3 shows the association between self-selected walking speed and ECw across different causes and levels of amputation and people without an amputation. Average preferred walking speed for each group was as follows; transfemoral vascular: 0.62 ± 0.11 m s^{-1}; transfemoral non-vascular: 1.02 ± 0.20 m s^{-1}; transtibial vascular: 0.82 ± 0.15 m s^{-1}; transtibial non-vascular: 1.20 ± 0.51 m s^{-1}. ; Results indicate that ECw is moderately to strongly associated with self-selected walking speed in all subgroups, as shown by the R^2 values. It can be observed that especially persons with an amputation due to vascular reasons generally walk below their most economic walking speed, which contributes to their increase in ECw compared to persons without an amputation. Note that the variation in ECw that could be accounted for by differences in walking speed (i.e. a shift of a specific group on their speed-ECw curve to the left ascending flank) seems substantial relative to the variation accounted for by cause or level of amputation alone (i.e. an upward shift of the speed-ECw curves between groups).

[insert Figure 3]

Discussion

The aim of this study was to provide quantitative estimates of differences in ECw between people with and without a lower limb amputation and to investigate the influence of cause of amputation, level of amputation and walking speed using a systematic review and meta-analysis of previous literature. In agreement with our expectations and previous research,[6] the results of this study showed that ECw is significantly higher in people with an amputation who walk with a lower limb prosthesis compared to people without an amputation (35%). On average, the difference in ECw is most pronounced in people with a transfemoral amputation due to vascular reasons (102%), followed by non-vascular transfemoral amputation (41%), vascular transtibial amputation (36%) and lowest after non-vascular transtibial amputation (12%). Furthermore, results suggest that reductions in self-selected walking speed seem to be a major contributor to the higher ECw in people with an amputation.

In total, we included 25 articles in the meta-analysis, which described 37 comparisons between designated subgroups of people with a lower limb amputation and people without an amputation. These comparisons were, however, not distributed equally between subgroups. Specifically, people with amputations due to vascular problems were under-represented in literature. Only four articles in the meta-analysis investigated ECw for persons with a vascular amputation, together including 47 persons with an amputation. From these articles data on three vascular-transtibial groups (n=23) and three vascular-transfemoral groups (n=24) could be derived. It should be acknowledged that this limited amount of data reduces the reliability of the estimates for these subgroups. Please note that most articles that were only included in the descriptive synthesis showed similar results to those in the meta-analysis, both in terms of ECw as in terms of relative underrepresentation of people with vascular amputation.

Generally, the results of our meta-analysis are in agreement with the study of Waters et al.,[6] as both studies indicate the highest ECw for persons with a vascular transfemoral amputation and the lowest ECw for non-vascular transtibial amputations. Although the current meta-analysis shows that people with an amputation have higher ECw compared to people without an amputation these differences were smaller than those reported by Waters et al.[6] Waters et al.[6] reported the highest ECw values amongst all included studies for each single subgroup of people with an amputation. Where Waters et al.[6] reported an increase between 25 and 120%, we found an average increase between 12 and 102%. This overestimation could be a result from the relatively small population studied by Waters et al.,[6] which might not have been fully representative for the general population of people with a lower limb amputation. Additionally, improved rehabilitation and/or prosthetic technology in recent years may have contributed to these different estimates. Worthy of note, however, no clear trend between year of publication and differences in energy cost can be observed among the included studies (Fig 2). Albeit that we only included studies at self-selected comfortable walking speed while the advantages of some modern prostheses have been shown to be more apparent at slow or high walking speeds.[40]

Our results show that self-selected walking speed partly accounts for the higher ECw in people with a lower limb amputation. The relation between walking speed and ECw can be modelled as a U-shaped function.[41, 42] For healthy individuals without an amputation costs are minimal around 1.2 m s^{-1} but rise rapidly at lower and faster walking speeds. Figure 3 provides additional insight in the effect of walking speed on ECw by visualising the position of the curves of all subgroups relative to each other. The coefficients of these curves do not have a physiological meaning, but only serve to describe the relationship between self-selected walking speed and ECw for each of the subgroups. It is expected that the speed-ECw curves of people with a lower limb amputation are shifted upwards as a consequence of reduced gait economy.[25] Figure 3 demonstrates that irrespective of such an upward shift, a substantial part of the difference in ECw at self-selected walking speed is due to the fact that people with a lower limb amputation, and especially those with a vascular cause of amputation, walk at slow speeds on the steeply ascending side of the speed-ECw curve. Hence, differences in ECw at self-selected walking speed between groups could partly be explained by their lower self-selected walking speeds, next to the upward shift of the speed-ECw curve. Note that an accurate analysis of the speed-ECw curves could not be performed in this study as data of subgroups were not available over comparable and full ranges of the walking speed spectrum. Therefore, we cannot draw definitive conclusions on the potential upward shift or shift in most economic speed for these subgroups.

Previous studies have shown that for people with a lower limb amputation, especially those with vascular cause of amputation and transfemoral amputation, preferred walking speed is generally slower than their most economic speed.[25, 26] People might reduce speed due to balance problems and associated fear of falling,[43] but it has been shown that the reduction in walking speed might also be related to energetic limitations. People with a lower limb amputation generally have a reduced aerobic capacity, especially people with a vascular cause of amputation.[44] The combination of reduced capacity and high demand increases the relative aerobic load at a given walking speed, which is known to affect quality of life in people with a lower limb amputation.[8] Reducing self-selected walking speed may therefore be necessary to maintain aerobic load within sustainable limits, i.e. at an acceptable percentage of maximal aerobic capacity.[6, 26] Yet this comes at the expense of walking economy. Consequently, next to level and cause of amputation, self-selected walking speed (and underlying factors such as physical fitness and fear of falling) needs to be taken into account as an important predictor of the ECw of individuals with lower limb amputation.

Our current review complements recent work by van Schaik et al.,[45] who performed a systematic review and meta-analysis of the metabolic requirement of daily activities, including walking, in people with lower limb amputation. In contrast to our analysis, this earlier study used energy consumption per unit of time (ml O_2 kg^{-1} min^{-1}) as outcome of interest. In agreement with our results they found a significant effect of level of amputation on energy requirement of walking, but no effect of cause of amputation was found. This was attributed to the low number of studies reporting on people with vascular cause of amputation. Van Schaik et al.[45] showed that walking at slower speeds resulted in lower energy consumption per unit of time – which is in line with the idea that people with a lower limb amputation probably walk slower to reduce the relative aerobic load of walking. However, when energy consumption is expressed per unit of time it is ignored that such a decrease in walking speed reduces walking economy (i.e. energy cost per unit distance). Our current review thus provides further important insights into the effects of reduced preferred walking speed on energy cost of people with different levels and causes of amputation. In addition, we also show how slower self-selected walking speed in persons with an amputation is related to an increase in energy cost, both as function of level and cause of amputation, which was not available in the study by van Schaik et al.[45]

Limitations

One main limitation of the current review is the heterogeneity of the included studies in terms of group size, participant characteristics (e.g. age, time since amputation) and study characteristics (e.g. walking speed and duration, treadmill versus overground walking). Our risk of bias assessment highlights the importance of standardising measurement protocols and measuring and reporting possible confounding factors. This heterogeneity– which has also been discussed by others[7, 45, 46] - could explain the considerable range of estimates for increased ECw at preferred walking speed between studies. Moreover, this heterogeneity may influence the accuracy of our estimates, when factors such as group size, participants and study characteristics were not distributed equally over the different subgroups. Although there were not enough studies available to statistically investigate the effect of such factors, inspection of the included studies did not point to clear systematic differences in these factors between subgroups. Our second limitation is related to converting all outcomes into the same unit. The applied equations included some assumptions about resting metabolism and RER. In Equation (1), RER was assumed to be equal to 1, this value might be slightly too high to achieve during walking for people with an amputation. However, Equation (1) was applied to only 3 studies in *analysis 1* and 6 studies in *analysis 2.* Moreover, effect of lower bound RER values would not exceed 5% in ECw, and would not have affected our overall conclusions. A final limitation pertains to the fact that this systematic review was not prospectively registered with PROSPERO, which would in hindsight have been preferred.

Further research

The current meta-analysis provides quantitative estimates of ECw in people with a lower limb amputation with different causality and at different levels. However, the reliability of these results may be affected by the heterogeneity of the studies that were combined. Therefore, future research should clearly report and standardise factors such as walking speed, walking surface and duration of the walking trial. Moreover, the risk of bias assessment shows the importance of reporting possible matching possibly confounding factors such as age and physical fitness when comparing different groups of persons with and without amputations, and of providing detailed information regarding data analysis (i.e. walking at steady-state and calculation of ECw). Related to this, there is a clear need for studies that investigate the interaction of level and cause of amputation and walking speed within a single study. This is essential to better understand the effects of these factors on the ECw after amputation. Furthermore, future research should especially focus on the ECw and walking speed of people with an amputation due to vascular reasons, since data for this specific patient group is scarce while the incidence of dysvascular amputation is the highest of all causes in Western countries. This group is also known to have limited exercise capacity, which compounds the negative effects of high aerobic demand of walking for regaining walking ability.[26, 44]

Conclusion

This systematic review provided updated quantitative estimates of energy cost of walking (ECw) of people with a lower limb amputation at their preferred walking speed, stratified for level and cause of amputation. Based on our meta-analysis, differences in ECw of +12% and +41% were found for people with non-vascular transtibial and transfemoral amputations compared to people without an amputation, respectively, and more pronounced differences in ECw were found for people with vascular transtibial (+36%) and transfemoral amputations (+102%). Moreover, our data suggest that a slow preferred walking speed may be a key factor for the observed increase in ECw in people with a lower limb amputation. The estimates provided in this review study can be used as reference values in clinical practice, to improve patient expectations, guide clinical decision making and benchmark prosthetic developments.

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Author contribution

XX carried out the data collection, analysis and writing of the article. YY conceived the general idea of this article and contributed to writing and proofing of the manuscript. ZZ performed RevMan data analysis and contributed to writing and proofing the manuscript.

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APPENDIX 1 – Search strategy

#1 - ENERGY COST	Energy AND (Cost OR Consumption OR Expenditure)
#2 - POPULATION	Amputation OR Amputees OR Artificial limbs OR Prosthesis
#3 - GAIT	Walking OR Gait OR Ambulation OR Locomotion
#4 – COMBINED	#1 AND #2 AND #3

APPENDIX 2 – Overview study populations

Analysis 1

	Controls			People with an amputation						
Study	**N**	**Age (years)**	**v (m/s)**	**N**	**Cause**	**Level**	**Age (years)**	**Gender**	**v (m/s)**	**Prosthesis**
Carse et al.[47]	10	51 ± 9	1.41 ± 0.1	8	Vascular	TF	60.8 ± 10.5	-	0.66 ± 0.24	Several types of knee, socket and suspension
				32	Non-vascular	TF	54.0 ± 12.5	-	0.92 ± 0.20	Several types of knee, socket and suspension
Chin et al.[48]	14	25.2 ± 4.0	1.50	8	Non-vascular	TF	22.5 ± 3.3	6/2	1.17	Intelligent prosthesis
Esposito et al.[18]	13	26.5 ± 6.0	1.21 ± 0.02	13	Non-vascular	TT	28.9 ± 5.3	13/0	1.20 ± 0.04	Energy storage and return prosthetic foot
Gailey et al.[49]	10	34.0 ± 12.9	1.27	10	Non-vascular	TT	37.8 ± 10.4	10/0	1.27	-
Gailey et al.[50]	10	33.2 ± 9.57	1.12	10	Non-vascular	TF	37.2 ± 11.0	10/0	1.12	CAT-CAM socket design
				10	Non-vascular	TF	34.6 ± 9.83	10/0	1.12	QUAD socket design
Ganguli et al.[51]	16	28.4 ± 7.05	0.83	10	Non-vascular	TT	29.9 ± 11.0	10/0	0.83	Patellar Tendon-Bearing
Gardinier et al.[52]	10	48.4 ± 16.62	1.28 ± 0.1	10	Non-vascular	TT	46.5 ± 14.9	10/0	1.28 ± 0.12	Unpowered prosthesis

										Powered prosthesis
Genin et al.[25]	13	27.8 ± 5.2	1.41 ± 0.02	9	Non-vascular	TT	35.3 ± 7.2	9/0	1.39 ± 0.17	KMB or Iceross socket
				10	Non-vascular	TF	34.7 ± 5.1	10/0	1.05 ± 0.05	CAT-CAM or QUAD
Gitter et al.[53]	8	31.8	1.36 ± 0.13	8	Non-vascular	TF	37.3	-	1.20 ± 0.10	-
Gjovaag et al.[54]	12	43.0 ± 11.7	1.44 ± 0.13	12	Non-vascular	TF	42.8 ± 13.5	6/6	0.88 ± 0.18	Microprocessor knee joint
Gjovaag et al.[55] *	8	39.0 ± 12.3	1.52 ± 0.15	8	Non-vascular	TF	37.0 ± 10.9	4/4	1.22 ± 0.19	Microcontroller knee joint and Hydraulic knee joint
Houdijk et al.[9]	11	47 ± 11	1.52 ± 0.21	3	Vascular	TT	46 ± 9	-	1.31	Dynamic foot
				8	Non-vascular	TT			1.33	
Hsu et al.[56]	18	27.5 ± 5.12	1.56	5	Non-vascular	TT	31.6 ± 4.28	5/0	1.34	FlexFoot *SACH/ Reflex VSP*
Hunter et al.[57]	10	30.7 ± 5.6	1.34	7	Non-vascular	TT	35.3 ± 5.2	-	1.34	-
IJmker et al.[58]	15	56.7 ± 12.4	1.10 ± 0.13	12	Non-vascular	TF	53.7 ± 13.0	7/4	0.73 ± 0.20	-
				15	Non-vascular	TT	57.3 ± 13.8	10/2	0.95 ± 0.17	-

Jarvis et al.[59] *	10	30 ± 6	1.29 (1.25-1.33)	10	Non-vascular	TF	29 ± 3	-	1.22 (1.08-1.36)	Hydraulic polycentric knee unit, elastic response foot
				10	Non-vascular	TT	28 ± 4	-	1.36 (1.28-1.44)	Hydraulic polycentric knee unit, elastic
Mengelkoch et al.[21]	3	35.3 ± 9.0	1.37 ± ???	3	Non-vascular	TT	35.3 ± 10	3/0	1.07 ± ???	SACH foot *Renegade/ Nitro ESAR*
Mengelkoch et al.[60]	3	27.0 ± 7.8	1.37 ± ???	3	Non-vascular	TF	27.7 ± 8.1	3/0	0.97 ± ???	SACH foot *Renegade/ Nitro ESAR*
Paysant et al.[23]	20	39.7	1.52 ± 0.11	10	Non-vascular	TT	39.2	10/0	1.49 ± 0.15	Silicon liners and suspension sleevers, energy storage foot
Russell-Esposito[19]	14	26 ± 6	1.34 ± 0.16	14	Non-vascular	TF	27 ± 5	-	1.23 ± 0.20	Knee: Genium, C-leg, Total Knee; Feet: several types (N=8; Trias, Re-Flex, Re-Flex Rotate, etc.)
Russell-Esposito[61]	8	29.4 ± 3.8	1.19 ± 0.11	8	Non-vascular	TT	32.9 ± 5.7	8/0	1.16 ± 0.09	Passive-dynamic, energy-storage-and-return foot
Russell-Esposito[62]	6	23 ± 5	1.21 ± 0.03	6	Non-vascular	TT	29 ± 6	5/1	1.24 ± 0.05	Energy-storage-and-return
Starholm et al.[24]	8	39.0 ± 12.3	1.52 ± 0.10	8	Non-vascular	TF	37.0 ± 10.9	4/4	1.22 ± 0.10	Several types of prosthesis (N=6; microprocessor knee, carbon foot etc.)
Waters et al.[6]	10	Range: 30-70	1.37 ± ???	13	Vascular	TF	60	-	0.60 ± 0.25	Total contact quadrilateral socket
				13	Vascular	TT	63	-	0.75 ± 0.15	Patellar tendon bearing socket

				15	Non-vascular	TF	31	-	0.87 ± 0.23	Total contact quadrilateral socket
				14	Non-vascular	TT	29	-	1.18 ± 0.17	Patellar tendon bearing socket
Wezenberg et al.[26]	21	60.80 ± 5.90	1.25 ± 0.15	15	Non-vascular	TT	60.3 ± 7.4	9/6	1.04 ± 0.18	-
				11	Non-vascular	TF	61.4 ± 4.1	10/1	0.86 ± 0.15	-
				7	Vascular	TT	66.9 ± 6.2	6/1	0.73 ± 0.24	-
				3	Vascular	TF	65.0 ± 6.2	2/1	0.63 ± 0.06	-
Analysis 2										
Askew et al.[63]				9	Non-vascular	TT	41.3 ± 14.3	9/0	0.98	Dynamic response foot with rigid ankle Dynamic response foot with hydraulic ankle
Barth et al.[64]				3	Vascular	TT	64	3/0	0.75 ± 0.01	Soft removable liner
				3	Non-vascular	TT	39.3	3/0	1.07 ± 0.06	Soft removable liner
Bell et al.[65]				10	Non-vascular	TF	32 ± 6.1	Unknown	1.11 ± 0.1	C-leg
				16	Non-vascular	TF			1.28 ± 0.2	C-leg
Bellmann et al.[66]				9	Non-	TF	35.4 ± 11	7/2	(1.0-1.2)	C-leg

		vascular					
Buckley et al.[67]	6	Non-vascular	TT	39.5 ± 9.9	6/0	0.89 ± 0.08	Total contact socket
Buckley et al.[68]	3	Non-vascular	TF	48.3 ± 10.1	3/0	0.70 ± 0.26	Conventional pneumatic swing phase control mechanism
							Intelligent prosthesis
Cao et al.[69]	6	Non-vascular	TF	36.8 ± 8.1	6/0	1.10	Intelligent prosthesis knee
Cassillas et al.[70]	12	Non-vascular	TT	50 ± 13.9	12/0	1.22 ± 0.13	SACH
							Energy storing and return foot
	12	Vascular	TT	73 ± 7	10/2	0.58 ± 0.11	SACH
							Energy storing and return foot
Darter & Wilken[71]	6	Non-vascular	TT	30 ± 4	5/1	1.34	Customary device
Darter et al.[72]	8	Non-vascular	TF	41.4 ± 12.1	5/3	1.12	Microprocessor knee unit
Detrembleur et al.[73]	7	Vascular	TT	50.5 ± 11	Unknown	0.80 ± 0.42	KMB socket or Iceross sockets with MultiFlex or FlexFoot
	7	Non-vascular	TF	38.5 ± 12	Unknown	0.67 ± 0.42	CAT-CAM socket or quadrilateral socket, both with various types of knees
Goktepe et al.[74]	32	Non-vascular	TT	28.1 ± 5.09	32/0	0.83	Patellar tendon bearing sockets

	9	Non-vascular	TF	30.1 ± 4.37	9/0	0.83	Quadrilateral of ischial containment socket with suction suspension
Grabowski et al.[75]	4	Non-vascular	TT	38-39	4/0	1.25	ESAR prosthesis *K3 Promotor foot*
Graham et al.[76]	6	Non-vascular	TF	40.3	6/0	1.00	MultiFlex Foot Energy storing and return foot
Houdijk et al.[16]	10	Non-vascular	TT	60.4 ± 18.3	7/3	1.28 ± 0.19	Various types of prosthetic feet, socket and suspension
	6	Vascular	TT	62.8 ± 10.2	6/0	1.02 ± 0.25	Various types of prosthetic feet, socket and suspension
	7	Non-vascular	TF	52.1 ± 10.7	7/0	1.21 ± 0.08	Various types of prosthetic feet, knees, socket and suspension
	3	Vascular	TF	59.7 ± 4.9	3/0	0.77 ± 0.35	Various types of prosthetic feet, knees, socket and suspension
Hsu et al.[77]	8	Non-vascular	TT	36 ± 15	8/0	1.19 ± 0.18	FlexFoot *Otto Bock C-Walk Foot/ SACH foot*
Kirker et al.[78]	6	Non-vascular	TF	36.5 ± 6.2	5/1	1.23 ± 0.17	Pneumatic, swing phase control
Lin-Chan et al.[79]	8	Non-vascular	TT	36 ± 15	8/0	1.33	60% of intact limb below-knee mass *80 or 100% of intact limb below-knee mass*

Macfarlane et al.[80]	5	Non-vascular	TF	36.8 ± 5.07	5/0	1.11	FlexFoot
McDonald et al.[81]	27	Non-vascular	TT	42.3 ± 11	22/5	0.96 ± 0.18	Energy Storing Foot *Crossover foot*
Orendurff et al.[82]	8	Non-vascular	TF	48.5 ± 10.2	7/1	1.31 ± 0.12	C-leg *Mauch SNS knee*
Rosenblatt et al.[83]	8	Non-vascular	TT	53.3 ± 13.0	7/1	1.23 ± 0.29	Vacuum Assisted Socket System *Non- Vacuum Assisted Socket System*
Schmalz et al.[84]	8	Non-vascular	TT	44 ± 17	Unknown	1.33 ± 0.08	Flex-Foot *Otto Bock foot*
	6	Non-vascular	TF	33 ± 6		1.11 ± 0.03	Optimal alignment (3R80)
Seymour et al.[85]	13	Non-vascular	TF	46 ± 13	11/2	0.82 ± 0.25	C-leg *Non-microprocessor control knee*
Smith & Martin[86]	6	Non-vascular	TT	47 ± 16	5/1	1.18 ± 0.12	Genesis II, College Park or FlexFoot
Starholm et al.[87]	8	Non-vascular	TF	46.63 ± 13.19	4/4	0.82 ± 0.21	C-leg or hydraulic knee joint and ICS socket or quadrilateral socket
Tekin et al.[88]	10	Non-vascular	TT	27.7 ± 5.31	10/0	0.83	-

Torburn et al.[89]	9	Non-vascular	TT	50.6 ± 15.6	9/0	1.37 ± 0.28	Flex-Foot *SACH/ Carbon Copy II/ Seattle Lite/ Quantum*
	7	Vascular	TT	62 ± 8.3	7/0	1.03 ± 0.15	Flex-Foot
Traballesi et al.[90]	7	Non-vascular	TF	33.9 ± 9.4	6/1	1.10 ± 0.08	Ischial Containment Socket *Marlo Anatomical Socket*
Traballesi et al.[27]	8	Vascular	TT	56 ± 17	6/2	0.66 ± 0.26	Patellar tendon bearing hard socket ad energy storing foot
	16	Vascular	TF	61 ± 11	11/5	0.45 ± 0.17	Quad socket, polycentric knee joint and SACH foot

APPENDIX 3 – Overview study protocols

Analysis 1

Study	Speed	Ground	Protocol	VO_2 analysis
Carse et al.[47]	PWS	Overground; 12 m walkway	6 minutes walking, mean over last minute	Open circuit spirometry, breath by breath
Chin et al.[48]	Fixed	Track with circumference 100 m	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Esposito et al.[18]	PWS	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Gailey et al.[49]	Fixed	Treadmill	9 minutes walking, mean over last 3 minutes	Open circuit spirometry
Gailey et al.[50]	Fixed	Track with length 36 m	Measurement during last 3 minutes	Open circuit spirometry
Ganguli et al.[51]	Fixed	Track with length 1 km	20 minutes walking	Douglas bag gas analysis
Gardinier et al.[52]	PWS	Track with length 8 m	8 minutes walking, 150 s used for analysis	Open circuit spirometry, breath by breath
Genin et al.[25]	Fixed	Outdoor track with length 41 m	Walking as long as needed maintain steady state for 3 minutes	Open circuit spirometry, breath by breath
Gitter et al.[53]	PWS	Overground	-	Douglas bag gas analysis
Gjovaag et al.[54]	PWS	Treadmill	3 minutes walking, mean over last 30 seconds	Open circuit spirometry, breath by breath
Gjovaag et al.[55]	PWS	Track with length 40 m	7 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath

Houdijk et al.[9]	PWS	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Hsu et al.[91]	Fixed	Treadmill	4 minutes walking, mean over last minute	Open circuit spirometry, breath by breath
Hunter et al.[57]	Fixed	Treadmill	5 minutes walking, mean over last minute	Open circuit spirometry
IJmker et al.[58]	PWS	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Jarvis et al.[59]	PWS	Track with length 10 m	5 minutes walking, mean over last minute	Open circuit spirometry
Mengelkoch et al.[21]	PWS	Treadmill	Mean over last 20 seconds	Open circuit spirometry, breath by breath
Mengelkoch et al.[60]	PWS	Treadmill	Mean over last 20 seconds	Open circuit spirometry, breath by breath
Paysant et al.[23]	PWS	Overground	10 minutes walking, mean over last 2 minutes	Open circuit spirometry
Russell-Esposito[19]	PWS	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Russell-Esposito[61]	PWS	Treadmill	8 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Russell-Esposito[62]	PWS	Level ground	6 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Starholm et al.[24]	PWS	Track with length 40 m	7 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Waters et al.[6]	PWS	Track with circumference 60.5 m	5 minutes walking, mean over last 2 minutes	Douglas bag analysis

Wezenberg et al.[26]	PWS	Treadmill	4 minutes walking, in order to reach steady-state	Open circuit spirometry, breath by breath
Analysis 2				
Askew et al.[63]	Fixed	Treadmill	7 minutes walking, mean over last 2 minutes	Open circuit spirometry
Barth et al.[64]	PWS	Treadmill	10 minutes walking, mean over last 3 minutes	Open circuit spirometry, breath by breath
Bell et al.[65]	PWS	Track, length 65 m	10 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Bellmann et al.[66]	PWS	Level ground	5 minutes walking, mean over last minute	Open circuit spirometry, breath by breath
Buckley et al.[67]	PWS	Treadmill	6 minutes walking, mean over last 3 minutes	Open circuit spirometry
Buckley et al.[68]	PWS	Treadmill	6 minutes walking, mean over 30 second intervals	Open circuit spirometry, breath by breath
Cao et al.[69]	Fixed	Treadmill	3 minutes walking	Open circuit spirometry, breath by breath
Casillas et al.[70]	PWS	Flat indoor surface	8 minutes walking, mean over last 2 minutes	Douglas bag
Darter & Wilken[71]	Fixed	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Darter et al.[72]	Fixed	Treadmill	4 minutes walking, mean over last minute	Open circuit spirometry, breath by breath
Detrembleur et al.[73]	PWS	Treadmill	Walk 2 minutes after steady-state was reached	Open circuit spirometry, breath by breath

Goktepe et al.[74]	Fixed	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Grabowski et al.[75]	Fixed	Treadmill	9 minutes walking, mean over last 4-6 minutes	Open circuit spirometry
Graham et al.[76]	Fixed	Treadmill	2 minutes walking, mean over last 20 seconds	Open circuit spirometry, breath by breath
Houdijk et al.[16]	PWS	Overground	4 minutes walking, mean over last 2 minutes	Open circuit, spirometry, breath by breath
Hsu et al.[77]	PWS	Treadmill	4 minutes walking, mean over last minute	Open circuit spirometry, breath by breath
Kirker et al.[78]	PWS	Treadmill	4 minutes walking	Closed system
Lin-Chan et al.[79]	Fixed	Treadmill	4 minutes walking, mean over last minute	Open circuit spirometry, breath by breath
Macfarlane et al.[92]	Fixed	Overground	-	Open circuit spirometry
McDonald et al.[81]	PWS	Treadmill	6 minutes walking, mean over last 3 minutes	Open circuit spirometry, breath by breath
Orendurff et al.[82]	PWS	Overground	Walking until 2 minutes of steady-state were reached	Open circuit spirometry, breath by breath
Rosenblatt et al.[93]	PWS	Overground	6 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Schmalz et al.[84]	PWS	Treadmill	5 minutes walking, mean over last 30 seconds	Open circuit spirometry, breath by breath
Seymour et al.[85]	PWS	Treadmill	3 minutes walking, mean over last 30 seconds	Open circuit spirometry, breath by breath

Smith & Martin[86]	PWS	Treadmill	10 minutes walking, mean over last 2 minutes	Open circuit spirometry
Starholm et al.[87]	PWS	Treadmill	10 minutes walking, mean over last 5 minutes	Open circuit spirometry, breath by breath
Tekin et al.[88]	Fixed	Treadmill	5 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Torburn et al.[89]	PWS	Track, length 60.5 m	5 to 20 minutes walking, mean over minutes 4 to 5, 9 to 10, 14 to 15 and 19 to 20	Open circuit spirometry, breath by breath
Traballesi et al.[90]	PWS	Track, length 61 m	7 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath
Traballesi et al.[27]	PWS	Track, length 61 m	7 minutes walking, mean over last 2 minutes	Open circuit spirometry, breath by breath

APPENDIX 4 – Modified Newcastle-Ottawa Scale

Selection

1) Representativeness of patient group (1)
   - *One star was awarded when in- and exclusion criteria were described.*
2) Representativeness of patient group (2)
   - *One star was awarded when patient characteristics were described (i.e. age, sex, level of amputation, cause of amputation, type of prosthesis, time since amputation).*
3) Selection of patient group
   - *Studies that provided a detailed description of the recruitment of patients were awarded a star (where were patients included, how many patients were screened, and how many of them eventually participated).*
4) Selection of control group
   - *Studies that selected control subjects from the same community as people after amputation were awarded a star.*

Comparability

5) Comparability of groups (1)
   - *One star was awarded when possible confounders were reported. At least three of the following confounders should be obtainable: age, sex, physical fitness (e.g. BMI, hours of physical activity per week), preferred walking speed.*
6) Comparability of groups (2)
   - *One star was awarded when groups were matched with regard to possible confounders or if confounders were statistically corrected for. At least 1 of the 2 following should be taken into account: age and sex.*
7) Comparability of groups (3)
   - *One star was awarded when groups were matched with regard to physical fitness or physical activity level.*

Outcome

8) Assessment of outcome (1)
   - *One star was awarded if the applied protocol was clearly described in terms of instructions, duration and environment.*
9) Assessment of outcome (2)
   - *One star was awarded if the measurement methods were clearly described in terms of the system that was used for measuring oxygen consumption.*
10) Assessment of outcome (3)
    - *One star was awarded if the data analysis was clearly described in terms of using steady-state values, averaging oxygen consumption and duration of the analysed period.*
11) Follow-up adequacy
    - *One star was awarded if ≤ 10% of the subjects that were initially included dropped out of the study / were not included in the final analysis. If no information was provided on this specific topic this was indicated with a question mark.*

APPENDIX 5 – Risk of bias assessment

Analysis 1

Study	1	2	3	4	5	6	7	8	9	10	11	NOS score
Carse[47]	✵	✵	✵		✵	✵	✵	✵	✵	✵		9
Chin[48]	✵	✵				✵		✵	✵	✵	?	6
Esposito[18]	✵	✵			✵	✵		✵	✵	✵	?	7
Gailey[49]	✵	✵			✵	✵		✵	✵		?	6
Gailey[50]	✵	✵			✵	✵	✵	✵	✵	✵	?	8
Ganguli[51]						✵		✵	✵		?	3
Gardinier[52]	✵	✵	✵		✵	✵		✵	✵	✵	✵	9
Genin[25]								✵	✵		?	2
Gitter[53]					✵				✵		?	2
Gjovaag[54]	✵	✵			✵	✵	✵	✵	✵	✵	?	8
Gjovaag[55]	✵	✵			✵	✵	✵	✵	✵		?	7
Houdijk[9]	✵					✵		✵	✵		?	4
Hsu[56]	✵				✵	✵		✵	✵	✵	?	6
Hunter[57]						✵		✵	✵		?	3

IJmker[94]	✸				✸	✸	✸	✸	✸	✸	✸	8
Jarvis[59]	✸	✸			✸	✸		✸	✸		?	6
Mengelkoch[21]	✸	✸		✸	✸	✸	✸		✸		✸	8
Mengelkoch[60]	✸	✸		✸	✸	✸	✸		✸		✸	8
Paysant[23]	✸	✸			✸	✸	✸	✸	✸		?	7
Russell-Esposito[62]	✸	✸				✸		✸	✸	✸	?	6
Russell-Esposito[61]	✸	✸				✸		✸	✸	✸	?	6
Russell-Esposito[19]	✸			✸	✸	✸	✸	✸	✸	✸	✸	9
Starholm[24]	✸	✸		✸	✸	✸	✸	✸	✸	✸	?	9
Waters[6]	✸							✸	✸	✸	?	4
Wezenberg[26]	✸				✸	✸	✸	✸	✸	✸	✸	8
Analysis 2												
Askew[63]		✸						✸	✸	✸	?	**4**
Barth[64]	✸	✸						✸		✸	?	**4**
Bell[65]	✸							✸	✸	✸	?	**4**
Bellmann[66]	✸	✸						✸	✸	✸	✸	**6**
Buckley[67]		✸						✸	✸	✸	✸	**5**
Buckley[68]								✸	✸		✸	**3**

Cao[69]	✵				✵	✵		?	**3**
Casillas[70]	✵	✵			✵	✵		?	**4**
Darter & Wilken[71]	✵	✵			✵	✵	✵		**5**
Darter & Wilken[72]	✵	✵			✵	✵	✵		**5**
Detrembleur[73]	✵	✵				✵	✵		**4**
Goktepe[74]	✵	✵			✵	✵	✵	?	**5**
Grabowski[75]		✵			✵	✵	✵	?	**4**
Graham[76]	✵				✵	✵	✵	✵	**5**
Houdijk[16]	✵				✵	✵	✵	?	**4**
Hsu[77]	✵	✵			✵	✵	✵	✵	**6**
Kirker[78]	✵	✵			✵	✵		✵	**5**
Lin-Chan[79]	✵	✵			✵	✵	✵	?	**5**
Macfarlane[80]	✵	✵			✵	✵		✵	**5**
McDonald[81]	✵	✵			✵	✵	✵		**5**
Orendurff[82]					✵	✵			**2**
Rosenblatt[83]	✵		✵		✵	✵	✵	✵	**6**
Schmalz[84]	✵				✵	✵	✵	?	**4**
Seymour[85]	✵	✵			✵	✵	✵		**5**

Smith & Martin[86]	✵	✵		✵	✵	✵	**?**	**5**
Starholm[87]	✵	✵	✵	✵	✵	✵	**?**	**6**
Tekin[88]	✵			✵	✵	✵	**?**	**4**
Torburn[89]	✵			✵	✵	✵		**4**
Traballesi[90]	✵	✵		✵	✵	✵		**5**
Traballesi[27]	✵			✵	✵	✵	**?**	**4**

List of figures

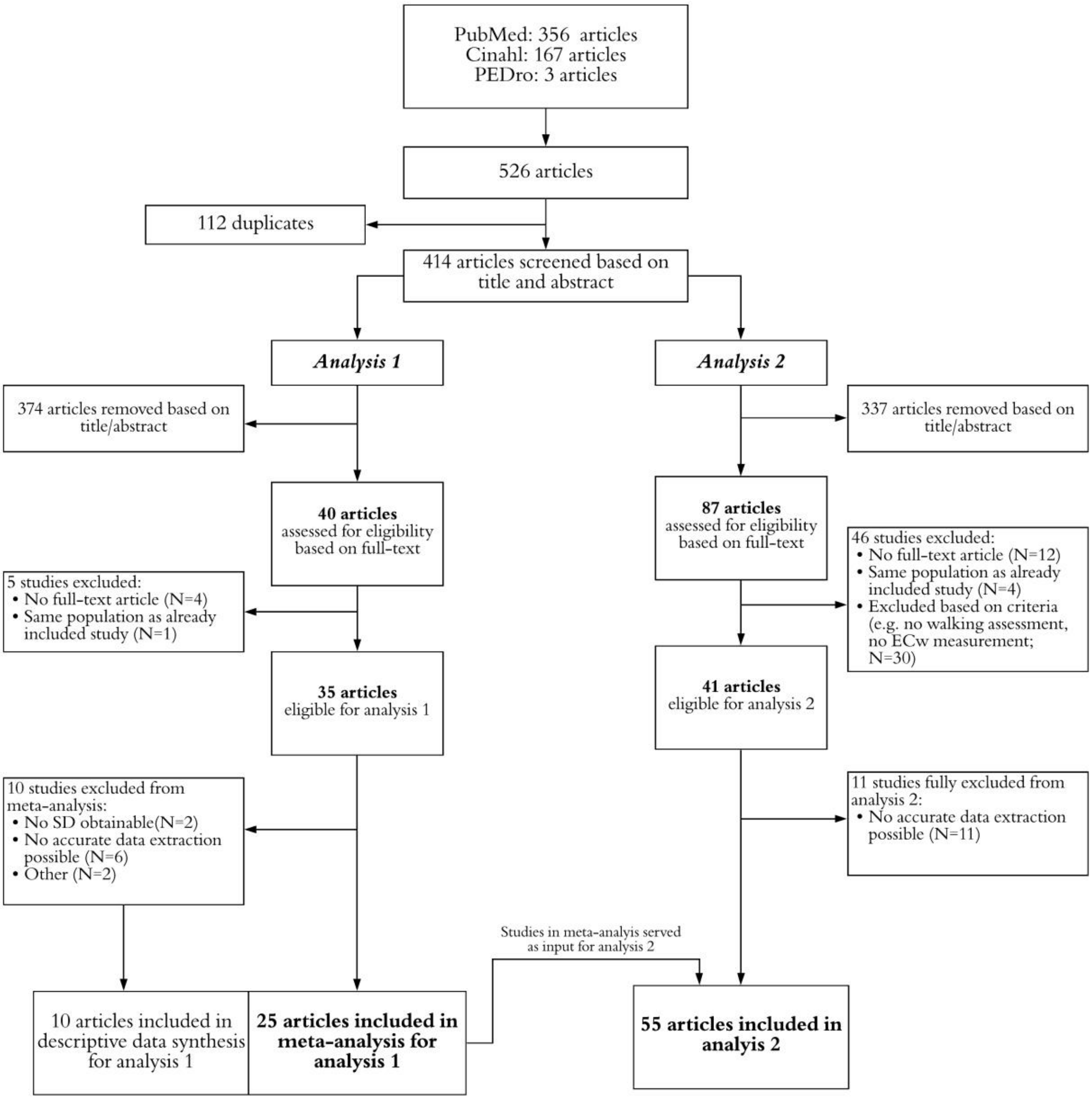

Figure 1. Flow-chart of inclusion of articles.

Study or Subgroup	Amputation Mean	Amputation SD	Amputation Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Transtibial - Non-vascular								
Esposito et al. (14), TT/ NV	0.1764	0.015	13	0.1763	0.0154	13	3.3%	0.00 [-0.01, 0.01]
Jarvis et al. (17), TT/ NV	0.1507	0.0298	10	0.146	0.0115	5	3.1%	0.00 [-0.02, 0.03]
Hsu et al. (00), TT/NV	0.19	0.0201	5	0.18	0.0212	18	3.1%	0.01 [-0.01, 0.03]
Russell-Esposito (17), TT/ NV	0.2148	0.0392	8	0.2028	0.0155	8	2.9%	0.01 [-0.02, 0.04]
Russell-Esposito (16), TT/ NV	0.1801	0.0121	6	0.168	0.0165	6	3.2%	0.01 [-0.00, 0.03]
Gardinier et al. (18), TT/ NV	0.1888	0.0247	10	0.1732	0.0104	10	3.2%	0.02 [-0.00, 0.03]
Paysant et al. (06), TT/ NV	0.163	0.015	10	0.147	0.02	20	3.3%	0.02 [0.00, 0.03]
Mengelkoch et al. (13), TT/ NV	0.219	0.062	3	0.199	0.041	3	1.3%	0.02 [-0.06, 0.10]
Gailey et al. (97), TT/ NV	0.168	0.0276	10	0.1474	0.0158	10	3.1%	0.02 [0.00, 0.04]
Genin et al. (08), TT/ NV	0.205	0.0157	9	0.1835	0.0181	7	3.2%	0.02 [0.00, 0.04]
Houdijk et al. (09), TT/NV	0.178	0.021	8	0.1468	0.0199	6	3.1%	0.03 [0.01, 0.05]
Wezenberg et al. (13), TT/NV	0.216	0.034	15	0.184	0.028	5	2.8%	0.03 [0.00, 0.06]
Hunter et al. (95), TT/ NV	0.2015	0.0174	7	0.1667	0.0063	10	3.3%	0.03 [0.02, 0.05]
IJmker et al. (14), TT/NV	0.229	0.033	12	0.1871	0.0256	7	2.9%	0.04 [0.02, 0.07]
Waters et al. (76), TT/ NV	0.2189	0.041	14	0.1585	0.0329	2	2.2%	0.06 [0.01, 0.11]
Ganguli et al. (75), TT/ NV	0.249	0.0444	10	0.188	0.0372	16	2.7%	0.06 [0.03, 0.09]
Subtotal (95% CI)			**150**			**146**	**46.9%**	**0.02 [0.01, 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 32.79, df = 15 (P = 0.005); I² = 54%								
Test for overall effect: Z = 5.35 (P < 0.00001)								
1.1.2 Transtibial - Vascular								
Houdijk et al. (09), TT/ V	0.186	0.021	3	0.1468	0.0199	5	2.9%	0.04 [0.01, 0.07]
Wezenberg et al. (13), TT/V	0.234	0.026	7	0.184	0.028	6	2.9%	0.05 [0.02, 0.08]
Waters et al. (76), TT/ V	0.26	0.0356	13	0.1585	0.0329	3	2.4%	0.10 [0.06, 0.14]
Subtotal (95% CI)			**23**			**14**	**8.2%**	**0.06 [0.03, 0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 5.92, df = 2 (P = 0.05); I² = 66%								
Test for overall effect: Z = 3.59 (P = 0.0003)								
1.1.3 Transfemoral - Non-vascular								
Jarvis et al. (17), TF/ NV	0.1817	0.0419	10	0.146	0.0115	5	2.9%	0.04 [0.01, 0.06]
Gitter et al. (95), TF/ NV	0.19	0.02	8	0.15	0.02	8	3.1%	0.04 [0.02, 0.06]
Chin et al. (03), TF/ NV	0.235	0.034	8	0.193	0.036	14	2.8%	0.04 [0.01, 0.07]
Starholm et al. (16), TF/ NV	0.2158	0.0478	8	0.1601	0.0208	8	2.6%	0.06 [0.02, 0.09]
Gailey et al. (93), TF/ NV_1	0.225	0.0281	10	0.1649	0.028	5	2.8%	0.06 [0.03, 0.09]
Gjovaag et al. (14), TF/ NV	0.2172	0.0174	12	0.1544	0.034	12	2.8%	0.06 [0.03, 0.09]
Gjovaag et al. (18), TF/ NV	0.2311	0.0303	8	0.1551	0.0116	8	3.1%	0.08 [0.05, 0.10]
Mengelkoch et al. (17), TF/ NV	0.251	0.05	3	0.171	0.02	3	1.9%	0.08 [0.02, 0.14]
Russell-Esposito (18), TF/ NV	0.2602	0.0434	14	0.1779	0.0249	14	3.0%	0.08 [0.06, 0.11]
Wezenberg et al. (13), TF/NV	0.267	0.055	11	0.184	0.028	6	2.5%	0.08 [0.04, 0.12]
Waters et al. (76), TF/ NV	0.2471	0.0651	15	0.1585	0.0329	2	2.0%	0.09 [0.03, 0.14]
Carse et al. (20), TF/NV	0.2714	0.0761	32	0.18	0.02	5	2.8%	0.09 [0.06, 0.12]
Genin et al. (08), TF/ NV	0.2836	0.0443	10	0.1835	0.0181	6	2.8%	0.10 [0.07, 0.13]
IJmker et al. (14), TF/NV	0.304	0.096	11	0.1871	0.0256	8	1.9%	0.12 [0.06, 0.18]
Gailey et al. (93), TF/ NV_2	0.2824	0.0821	10	0.1649	0.028	5	2.0%	0.12 [0.06, 0.17]
Subtotal (95% CI)			**170**			**109**	**39.1%**	**0.07 [0.06, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 31.13, df = 14 (P = 0.005); I² = 55%								
Test for overall effect: Z = 10.78 (P < 0.00001)								
1.1.4 Transfemoral - Vascular								
Wezenberg et al. (13), TF/V	0.367	0.016	3	0.184	0.028	5	2.8%	0.18 [0.15, 0.21]
Carse et al. (20), TF/V	0.3661	0.1404	8	0.18	0.02	5	1.1%	0.19 [0.09, 0.28]
Waters et al. (76), TF/ V	0.35	0.0806	13	0.1585	0.0329	3	2.0%	0.19 [0.13, 0.25]
Subtotal (95% CI)			**24**			**13**	**5.9%**	**0.18 [0.16, 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0%								
Test for overall effect: Z = 13.95 (P < 0.00001)								
Total (95% CI)			**367**			**282**	**100.0%**	**0.06 [0.04, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 307.42, df = 36 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 8.80 (P < 0.00001)								
Test for subgroup differences: Chi² = 165.92, df = 3 (P < 0.00001), I² = 98.2%								

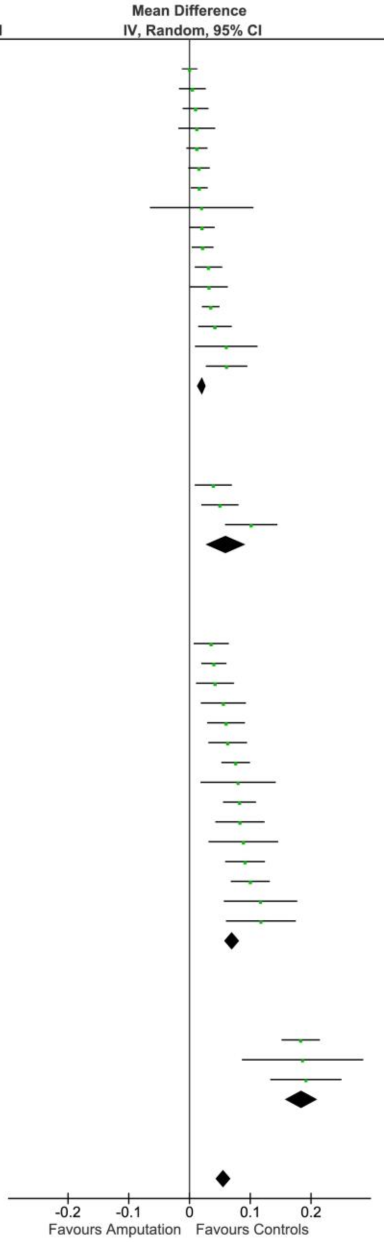

Figure 2. Pooled results of studies that investigated ECw in people with a lower limb amputation.

TF/NV = transfemoral, non-vascular amputation; TF/V = transfemoral, vascular amputation; TT/NV = transtibial, non-vascular amputation; TT/V = transtibial, vascular amputation. NB1:Average preferred walking speed for each group was as follows; transtibial non-vascular: 1.20 ± 0.51 m s^{-1}; transtibial vascular: 0.82 ± 0.15 m s^{-1}; transfemoral non-vascular: 1.02 ± 0.20 m $s^{--1;}$ transfemoral vascular: 0.62 ± 0.11 m s. NB2: For two of the included studies,[55, 59] standard deviation was obtained using Equation (2), as no other methods could be applied. However, this equation is typically recommend for studies with larger samples. To investigate whether using this equation influenced our results, we performed the meta-analysis also without these two studies, but this had minimal effect on the outcomes, and the main and subgroup remained unaffected.

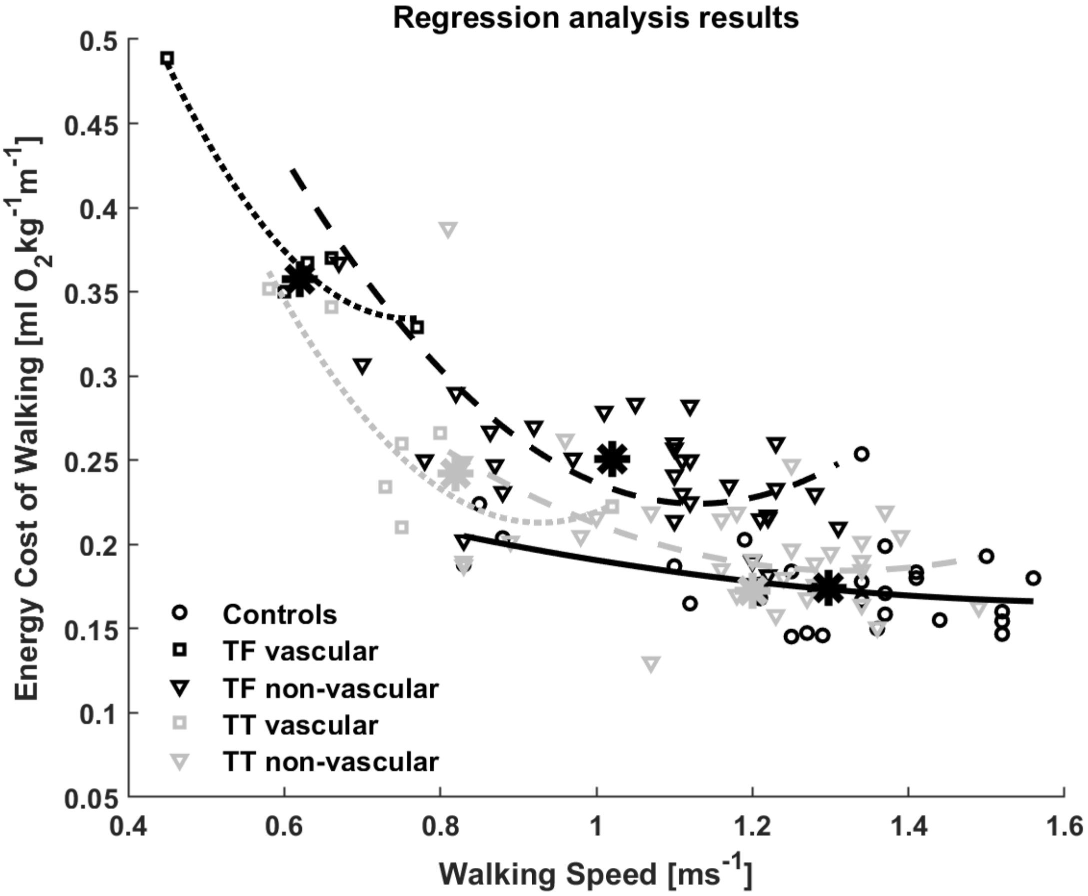

Figure 3. The effect of velocity on ECw. The average ECw and walking speed derived from analysis 1 is indicated with an asterisk (*) for each subgroup. CO = controls; TT = transtibial; TF = transfemoral. The values of the coefficients *a*, *b* and c represent the description of the second order polynomial function for each subgroup. CO: a=0.06, b=-0.19, c=0.32, R^2 =0.17; TF vascular: a=1.58, b=-2.40,c=1.24, R^2 = 0.93; TF non-vascular: a=0.73, b=-1.66, c=1.16, R^2 = 0.60; TT vascular: a=1.23, b=-2.28, c=1.27, R^2 = 0.75; TT non-vascular = a=0.27, b=-0.72, c=0.66, R^2 =0.27.

List of Tables

Table 1: overview of number of articles included in the different analyses by level and cause of amputation.

	Analysis 1 – influence of level and cause of amputation on ECw *(25 articles, describing 37 subgroups)*	**Analysis 2 – influence of walking speed on ECw** *(55 articles, describing 78 subgroups)*
Transfemoral – Vascular	3	5
Transfemoral – Non-Vascular	15	32
Transtibial – Vascular	3	9
Transtibial – Non-Vascular	16	32

NB: Please keep in mind that the number of articles and subgroups shown for *analysis 2* is equal to the sum of the articles in *analysis 1* and the additionally included articles in *analysis 2*.

Table 2. Overview of pairwise comparisons of ECw between different subgroups.

	Transfemoral – Vascular	*Transfemoral – Non-Vascular*	*Transtibial – Vascular*	*Transtibial – Non-Vascular*
Transfemoral – Vascular		$\chi^2(1)=60.05$ $p < 0.00001$* $I^2= 98.3\%$	$\chi^2(1)=33.78$ $p < 0.00001$* $I^2= 97\%$	$\chi^2(1)=141.11$ $p < 0.00001$* $I^2= 99.3\%$
Transfemoral – Non-Vascular			$\chi^2(1)=0.30$ $p = 0.580$ $I^2= 0\%$	$\chi^2(1)=42.63$ $p < 0.00001$* $I^2= 97.7\%$
Transtibial – Vascular				$\chi^2(1)=5.28$ $p = 0.020$* $I^2= 81\%$
Transtibial – Non-Vascular				