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Impact of diabetes on medical costs in the pre- and postoperative year of lower extremity amputations in Belgium

Patrick Lauwers[a,b], Jeroen M. H. Hendriks[a,b], Kristien Wouters[c], Johan Vanoverloop[d], Hervé Avalosse[d,e], Eveline Dirinck[f,g*], Frank Nobels[h*], on behalf of the Belgian Amputation Group.

*Eveline Dirinck and Frank Nobels are joint senior authors.

[a]Antwerp University Hospital, Department of Thoracic and Vascular Surgery, Drie Eikenstraat 655, B-2650 Edegem, Belgium

[b]University of Antwerp, Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), Universiteitsplein 1, B-2610 Wilrijk, Belgium

[c]Antwerp University Hospital, Clinical Trial Centre (CTC), CRC Antwerp, Drie Eikenstraat 655, B-2650 Edegem, Belgium

[d]Intermutualistisch Agentschap/Agence Intermutualiste (IMA/AIM), Bolwerklaan 21 B 7, B-1210 Brussels, Belgium

[e]Landsbond der Christelijke Mutualiteiten/Alliance Nationale des Mutualités Chrétiennes, Haachtsesteenweg 579 B 40, B-1031 Brussels, Belgium

[f]Antwerp University Hospital, Department of Endocrinology, Diabetology and Metabolism, Drie Eikenstraat 655, B-2650 Edegem, Belgium

[g]University of Antwerp, Laboratory of Experimental Medicine and Paediatrics (LEMP), Universiteitsplein 1, B-2610 Wilrijk, Belgium

[h]Onze Lieve Vrouw Ziekenhuis Aalst, Department of Endocrinology, Moorselbaan 164, B-9300 Aalst, Belgium

The Belgian Amputation Group includes the following collaborators:

Isabelle Dumont, MD, Centre Multidisciplinaire du Pied Diabétique, Place L. Delhaize 31, B-6043 Ransart, Belgium

Patricia Felix, MD, Hôpital Citadelle, Department of Endocrinology, Boulevard du 12[e] de Ligne, B-4000 Liège, Belgium

Giovanni Matricali, PhD, Leuven University Hospital, Department of Orthopaedic Surgery, Herestraat 49, B-3000 Leuven, Belgium

Corresponding author:

Patrick Lauwers, Antwerp University Hospital, Department of Thoracic and Vascular Surgery,

Drie Eikenstraat 655, B-2650 Edegem, Belgium; patrick.lauwers@uza.be, +32 3 821 43 61.

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Highlights

- Individuals undergoing amputation cost much more than amputation-free comparators.
- Diabetes has a significant impact on costs both before and after amputation.
- The impact of diabetes on medical costs fades away with higher amputation levels.
- Individuals undergoing more than one amputation generate significantly higher costs.

Abstract

Aims: To compare the medical costs of individuals undergoing lower extremity amputation (LEA) in Belgium with those of amputation-free individuals.

Methods: Belgian citizens undergoing LEAs in 2014 were identified. The median costs per capita in euros for the 12 months preceding and following minor and major LEAs were compared with those of matched amputation-free individuals.

Results: A total of 3324 Belgian citizens underwent LEAs (2295 minor, 1029 major), 2130 of them had diabetes. The comparison group included 31,716 individuals. Amputation was associated with high medical costs (individuals with diabetes: major LEA €49,735, minor LEA €24,243, no LEA €2,877 in the year preceding amputation; €45,740, €21,445 and €2,284, respectively, in the post-amputation year). Significantly higher costs were observed in the individuals with (versus without) diabetes in all groups. This difference diminished with higher amputation levels. Individuals undergoing multiple LEAs generated higher costs (individuals with diabetes: €39,313–€89,563 when LEAs preceded index amputation; €46,629–€92,877 when LEAs followed index amputation). Individuals dying in the year after a major LEA generated remarkably lower costs.

Conclusions: LEA-related medical costs were high. Diabetes significantly impacted costs, but differences in costs diminished with higher amputation levels. Individuals with multiple amputations generated the highest costs.

Keywords: Diabetes mellitus, Diabetic foot, Medical costs, Medical expenditure, Lower extremity amputation, Belgium

1. Introduction

Lower extremity amputations (LEAs), whether major or minor amputations, are associated with significantly reduced quality of life, high morbidity and mortality and a high financial burden [1]. In Western countries, most amputations are performed in the context of diabetic foot disease and/or peripheral arterial disease [2, 3]. Data from the National Health Service in England for 2014–2015 estimated expenditure of £837 million to £962 million on health-care costs related to foot ulceration and all amputations in individuals with diabetes, equivalent to 0.78%–0.90% of the entire health service's budget [1]. As such, the costs associated with diabetic foot disease and diabetes-related amputations accounted for higher expenditure than the combined annual costs of the three most common cancers in the UK. Of these costs, 7% was attributed to amputation and post-amputation care [1]. Annually, the immediate health-care costs associated with the amputation of a limb, not including prosthetic or rehabilitation costs, total nearly $8 billion in the United States, and the five-year health-care costs associated with limb loss are estimated to be more than $500,000 per person, nearly double the lifetime health-care costs of an average person without limb loss [2].

In Belgium, with nationwide accreditation of multidisciplinary diabetic foot clinics since 2005 [4], there was a significant decline in the incidence rate of major LEAs in people with diabetes between 2009 and 2018 [5]. However, in England, the United States and Canada, no reduction or even a growing incidence of major LEAs have been observed [6–9]. Since large increases in diabetes prevalence have been observed in virtually all regions of the world [10] and in view of the increased incidence of peripheral arterial disease due to an ageing population [11, 12], further reduction in the number of amputations worldwide will be a challenge. Hence, studies on amputation costs are of utmost relevance for health-care decision-makers.

It is also relevant to analyse health-care costs both in the year preceding and the year following an amputation and not only the costs related to the index amputation and a short perioperative window [13–17]. Costs in the year preceding a minor or major LEA likely reflect the financial burden of the efforts undertaken to avoid the amputation, while costs in the year following a LEA reflect the postoperative period and intensive rehabilitation process, especially after a major LEA.

Many patients undergoing amputation have multiple comorbidities, including diabetes in particular. According to US data, the average annual medical costs of individuals with diabetes are significantly higher than those of individuals without diabetes [18]. Amputation is one of the costliest complications of diabetes. In a German study of 316,220 individuals with type 2 diabetes, LEA was the second most expensive diabetes-related complication after end-stage renal disease [19]. Therefore, the present study aimed to assess the impact of diabetes on all health-care-related costs in the year preceding and the year following amputation in Belgium. The median per capita medical costs of minor and major LEAs performed in Belgium in 2014 were studied and compared to the medical costs of an age- and sex-matched comparison group of individuals who remained amputation-free. In further analysis, the costs for individuals undergoing a single minor or major amputation were compared to the costs for individuals undergoing multiple amputations and with the costs for the individuals who died in the postoperative year.

2. Materials and Methods

2.1. Study population, comparison group and data collection

Nationwide data on lower extremity amputations (LEAs) were retrospectively collected from the InterMutualistisch Agentschap/Agence InterMutualiste (IMA/AIM). This non-profit organisation collects data on the reimbursement of all the medical acts provided by all Belgian national health insurance funds. Hence, this administrative database contains only reimbursement data but no clinical information. As Belgian citizens are obliged to join one of the national health insurance funds, this database covers the entire Belgian population.

First, a database including all persons who underwent LEA in Belgium from 1 January 2014 to 31 December 2014 was created. For all the individuals, data were available regarding the level of amputation, the presence of diabetes, age at intervention and gender [5]. The LEAs were coded according to the official nomenclature of the Belgian health authorities. Any amputation above the tarsometatarsal joints was considered 'major', while amputations involving the tarsometatarsal joints (Lisfranc amputation) or more distal, were considered 'minor'. The first amputation performed in 2014 was retained as an index amputation. If it was a minor amputation, the individual was included in the minor LEA group, and if it was a major amputation, the individual was included in the major LEA group. The presence of diabetes was deduced, since the database contains only reimbursement data and no clinical information. A person was considered to have diabetes if at least one of the following criteria was met: inclusion in a national diabetes care programme, treatment with diabetes-specific medication and/or repetitive HbA1c measurements (at least three measurements over a two-year period) [5]. Age was expressed in strata (0–39, 40–49, 50–59, 60–69, 70–79 and 80+ years).

Second, a comparison group of individuals without LEA was created. For every individual undergoing LEA in 2014, 10 citizens without LEA (5 with and 5 without diabetes) were randomly selected from the same age group, from the same gender and living in the same district.

Finally, all medical expenses reimbursed by the national health insurance funds during the 12 months preceding and the 12 months following the index amputation were collected. The median per capita costs of the periods preceding and following the LEA were presented separately as euros. For the comparison group of individuals who remained amputation-free, the median costs in the 12 months before and after the date of amputation of their matched individuals were counted. The costs included all costs related to paramedical, medical and surgical acts, hospitalisation, rehabilitation, outpatient care, drug prescriptions, preventive care and medical equipment, which were obtained from the website of the Belgian National Institute for Health and Disability Insurance (only available in Dutch and French). Indirect costs and non-reimbursed costs were not included.

The data selection requirements of the independent researchers were reviewed and approved by the Information Safety Committee of the IMA/AIM. The data were anonymised and aggregated by the IMA/AIM and analysed and interpreted by the independent researchers. Thus, individual written consent was not required.

2.2. Statistical analysis

Medical expenses were presented as median costs per capita in euros with lower and upper quartiles (25th and 75th percentiles) for the six subgroups (no LEA, minor LEA and major LEA, both in people with and without diabetes) for the 12 months preceding and the 12 months following a LEA.

A linear regression model with log transformation was used to identify the impact of diabetes, the level of the amputation (no LEA, a minor LEA or a major LEA), the age group (<40, 40–49, 50–59, 60–69, 70–79 and ≥80 years) and gender on medical expenses. Separate models were fitted for the preoperative and postoperative years. Interaction terms between diabetes and the type of LEA, diabetes and age group, diabetes and gender, the type of LEA and age group, the type of LEA and gender and gender and age group were added to the models. The medical expenses for the 12 months preceding and following an LEA were further explored in post hoc comparisons. The Bonferroni-Holm correction was used to adjust for multiple testing. The results were backtransformed and presented as fold changes of the geometric mean alongside 95% confidence intervals.

As individuals undergoing LEA are at high risk of secondary amputations and/or mortality [5, 20], a subgroup analysis was conducted according to different scenarios. For the costs in the 12 months preceding the index amputation, the following three scenarios were considered: no amputation versus at least one minor LEA (but no major LEA) versus at least one major LEA in the 12 months before the date of the index amputation. The results were compared between the individuals with and without diabetes using a linear regression model, as described above, where the level of amputation was replaced by the subgroup according to a history of a LEA in the preceding year.

For the costs in the 12 months following the date of the index amputation, the following three scenarios were considered: no further amputation; additional minor and/or major LEA(s); or death, and the most serious event was considered. The results were compared between the individuals with and without diabetes using a linear regression model, as described above, where the level of amputation was replaced by the subgroup according to events in the 12 months following the index amputation.

All analyses were conducted using R 3.6.0. Differences were considered significant when $p < 0.05$.

3. Results

3.1. Study population and comparison group

In 2014, 11,196,640 individuals were registered by the different Belgian health insurance funds spread over 44 administrative districts. Of these, 3342 Belgian citizens were confronted with at least one LEA [5]. For 18 persons, the required data were not available, leaving 3324 subjects available for analysis (Table 1): 2130 individuals with diabetes (minor LEA: 1554; major LEA: 576) and 1194 individuals without diabetes (minor LEA: 758; major LEA: 436).

For every individual undergoing LEA in 2014, 10 amputation-free Belgian citizens (5 with and 5 without diabetes) were randomly selected from the same age group of the same gender and living in the same district, resulting in a comparison group of 33,420 people. After removing duplicates, 32,599 unique subjects were retained. For 180 persons, the required data were not available, and 703 individuals died before the date of the LEA of their matched study individuals [20]. Thus, the final comparison group consisted of 31,716 individuals: 15,844 with and 15,872 without diabetes.

Table 1 presents the 3324 individuals undergoing amputation in 2014 and their 31,716 amputation-free comparators, categorised according to the scenarios in the 12 months preceding and the 12 months following their index procedure.

3.2. Medical costs in the 12 months preceding LEA (Tables 2a and 2b)

The median per capita medical costs in the 12 months preceding the index amputation are presented in Table 2a. Diabetes was significantly related with higher medical costs, both in the comparison group and in the group of individuals who underwent minor and major LEA. However, this difference in costs between the individuals with and without diabetes diminished progressively with higher amputation levels (a 3-fold increase for the individuals without a LEA, a 2.39-fold increase for the individuals with minor LEA and a 1.43-fold increase for the individuals with a major LEA as the index amputation, all highly significant) (Table 2a). In the individuals with diabetes, the costs in the year preceding the LEA were 6.21- and 16.42-fold higher for those undergoing minor and major LEA compared to those in the comparison group of individuals who remained amputation-free. For the individuals without diabetes, the costs were 7.79- and 27.36-fold higher for those undergoing minor and major LEA, respectively (all $p < 0.001$) (Table 2a).

One-quarter of the individuals who underwent their index minor or major LEAs in 2014 had a history of a minor or major LEA in the 12 months preceding their index amputation (841 individuals with a previous LEA versus 2483 individuals without; Table 1). The median costs in the 12 months preceding the index minor or major LEA were divided according to the three different scenarios described in the methods section: no amputation versus a minor or major LEA in the 12 months preceding the index amputation (Table 2b).

The individuals who underwent an amputation in the 12 months preceding the index minor or major LEA generated much higher costs compared to the individuals without a history of recent amputation (Table 2b). The individuals with diabetes generated statistically higher medical costs, both in the group without prior amputation and in the group of individuals who underwent one or more minor LEAs in the 12 months preceding their index amputation. The costs were highest for the individuals who underwent a major LEA in the year preceding their index amputation, but in this scenario, the difference in costs between the individuals with and without diabetes was no longer statistically significant (Table 2b).

3.3. Medical costs in the 12 months following LEA (Tables 3a and 3b)

The median per capita medical costs in the year following the index amputation are presented in Table 3a. In the 12 months following an LEA, diabetes was significantly related to higher medical costs, both in the comparison group and in the group of individuals who underwent minor and major LEA. This difference in costs between the individuals with and without diabetes diminished progressively with higher amputation levels (a 2.54-fold increase for the individuals without LEA, a 2.04-fold increase for the individuals with a minor LEA and a 1.54-fold increase for the individuals with a major LEA as the index amputation; all highly significant with $p < 0.001$) (Table 3a). In the individuals with diabetes, the costs in the year following a LEA were 8.68- and 22.33-fold higher for those undergoing minor and major LEAs compared to those in the comparison group of individuals who remained amputation-free. For the individuals without diabetes, the costs were 10.81- and 36.78-fold higher for those undergoing minor and major LEAs, respectively (all $p < 0.001$) (Table 3a).

Two-thirds of the individuals who underwent their index minor or major LEA in 2014 survived the first postoperative year without further amputations. However, 258 individuals underwent one (or more) secondary amputation(s), and 853 individuals died during the 12 months following their index amputation. The latter group also included 46 individuals who first underwent a secondary amputation but subsequently died (Table 1).

In Table 3b, the median costs in the year following the index minor or major LEA are divided according to the three scenarios described in the methods section. The individuals who underwent a LEA in the 12 months following their index minor or major LEA generated much higher costs than the individuals without a further amputation. In the group of individuals with secondary amputations, the difference in costs between the individuals with and without diabetes was no longer significant. In the group of individuals who died during follow-up, the difference in costs between the individuals with and without diabetes was highly significant. In the individuals who underwent a minor LEA as the index procedure but later died, medical costs were somewhat higher compared to those who survived the first 12 months after their amputation. When individuals had a major LEA as the index procedure but later died, the costs were much lower.

3.4. Comparison of medical costs in the 12 months before and after LEA

The median per capita medical costs in the 12 months following the index amputation compared to the medical costs in the year preceding the index amputation were comparable for the individuals who underwent a minor LEA and for the individuals without diabetes who underwent a major LEA

(Table 4). In the individuals with diabetes who had a major amputation as the index amputation, the medical costs were higher in the 12 months preceding the amputation (Table 4).

4. Discussion

National data on the medical costs of 3324 Belgian citizens who underwent a minor or major LEA in 2014 were reported and compared with the data of 31,716 citizens matched by age, sex and district who remained amputation-free. Four findings are eye-catching.

First, both major and minor LEAs incur high medical costs, much higher than the medical costs of an amputation-free comparator. The strength of this study is that it went beyond the cost of the surgical act itself and reported all-encompassing cost data, including costs related to chronic diseases such as diabetes. These data are reported both for individuals undergoing LEA and for those remaining amputation-free. This has the advantage that the data clearly reflect the financial impact on society. Comparable literature published since 2010 is scarce [1, 14–16, 19, 21–24]. Most of these studies are modelling studies simulating inpatient costs or mean annual costs following amputation. In contrast, the present study was based on real cost data over the 12 months following but also preceding the amputation. To the best of our knowledge, this is the first study to present real cost data at a national level. In addition, as individuals undergoing LEA are at high risk for secondary amputations and/or mortality [5, 20], a subgroup analysis taking into account further amputations and mortality was undertaken, which is novel in amputation research.

Second, medical costs were found to be high both in the year preceding and the year following the LEA. It is relevant to analyse longer-term health-care costs and not only to consider the inpatient costs related to an amputation. The costs in the 12 months preceding an amputation likely reflect the efforts undertaken in attempt to avoid the amputation, while the costs in the year following an amputation reflect the postoperative period and intensive rehabilitation process, especially after a major LEA. In the above-mentioned studies [1, 14–16, 19, 21–24], only inpatient costs or annual health-care costs were reported. In the present study, data on all reimbursed health-care costs during the 12 months preceding and the 12 months following the amputation are presented. A limitation was that no distinction between inpatient and outpatient costs was possible. Two authors have presented data using a similar study design, but in much smaller patient cohorts [25, 26]. Hoffmann et al. reported in

2013 all the direct medical costs of 444 individuals who underwent a first major LEA in Germany between 2005 and 2009, studying a period starting one year before the amputation and following patients up until three years afterwards [25]. In that study, the total costs in the year before a major LEA were higher in the individuals with diabetes (€24,504 versus €18,961). Remarkably, up to 24 weeks after an LEA, the costs were comparable for both the individuals with and without diabetes, indicating that the immediate postoperative costs were mainly driven by the LEA itself and not by the diabetes. After these first 24 weeks, the differences in costs between the individuals with and without diabetes increased again, with the costs in the year following an LEA being higher than the costs in the preoperative year (€55,668 versus €50,834) [25]. These findings contrast with our findings, in which costs in the year preceding a major LEA were higher than the costs in the year following an LEA in the individuals with diabetes. In another German study published in 2018, Kähm et al. observed that after a peak in the first quartile, the costs progressively diminished in the second, third and fourth quartiles of the year after an LEA. From the second postoperative year onwards, medical expenses remained stable at +/- €20,000 on a yearly basis [19]. In a US study by Stewart et al. published in 2022, health-care costs one year before and one year after an LEA were retrospectively reported for a cohort of 90 patients (including 76 minor and 14 major LEAs) [26]. Most of these individuals had diabetes (74%). The mean cost of the index hospitalisation per patient was $51,481; over the two-year period, the mean cost was $11,4292 per person [26].

Third, diabetes is associated with significantly higher additional costs. According to American Diabetes Association data, the average annual medical costs of individuals with diabetes are approximately 2.3-fold higher than those of individuals without diabetes [18]. This brings up another strength of the present study. In Belgium, as in other Western countries, diabetes is highly prevalent in individuals undergoing LEAs [5]. Nevertheless, other indications for LEA exist. It is remarkable that only sporadically cost comparisons between individuals with and without diabetes undergoing LEA have been reported. In a large US study of individuals treated for a foot ulcer, Hicks et al. found no difference with regard to in-hospital costs between individuals with and those without diabetes after minor and major amputations [22]. In contrast, Malone et al. observed higher inpatient costs in individuals with diabetes after minor and major amputations [16]. In the present study, diabetes significantly increased the health-care-related costs for the individuals who underwent minor and major LEAs, as in the comparison group.

Finally, although we found that diabetes was significantly associated with higher medical costs, the difference in costs between individuals with and without diabetes faded away with higher amputation levels, which is another novel finding in amputation research.

5. Conclusion

In the present study, LEA-related medical costs were significantly higher in individuals with diabetes compared to those without diabetes, both in the year preceding and the year following an LEA. This difference in medical costs between individuals with and without diabetes diminished with higher amputation levels. As diabetic foot disease is one of the main indications for LEA in Western countries, the prevention of diabetes and of diabetic foot disease in particular will reduce the strain on national health-care-related expenses.

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Author contributions

Conceptualisation of the study: PL, ED, FN, JH, HA, JVO

Literature search: PL

Data collection: HA, JVO

Data analysis: KW

Interpretation of analysis: KW, PL, ED, FN

Writing of the manuscript: PL, KW, ED, FN

Proofreading and text editing: PL, ED, FN, JH, HA, JVO

All co-authors have contributed to and approved this manuscript.

Data sharing:

Due to privacy regulations, data at the individual patient level and the assembled database are the property of the InterMutualistisch Agentschap/Agence InterMutualiste (IMA/AIM) and cannot be shared.

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Tables

Table 1. Events in the 12 months preceding (upper panel) and the 12 months following (lower panel) the index amputation.

		Events in the 12 months preceding the index LEA					
		No LEA		Minor LEA		Major LEA	
		Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
Index procedure	No LEA (n = 31716)	15844	15872				
	Minor LEA (n = 2312)	1187	651	348	94	19	13
	Major LEA (n = 1012)	323	322	144	43	109	71

		Events in the 12 months following the index LEA					
		No secondary LEA*		Secondary LEA*		Death**	
		Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
Index procedure	No LEA (n = 31716)	15064	15263			780	609
	Minor LEA (n = 2312)	1067	532	183	34	304	162
	Major LEA (n = 1012)	338	246	31	10	207	180

LEA: lower extremity amputation.

*Secondary LEA: additional minor and/or major LEA(s) in the 12 months following the index amputation.

**This group included a limited number of individuals who first underwent one or more secondary amputations but subsequently died.

Table 2a. Median medical costs for individuals with and without diabetes undergoing minor and major LEAs during the 12 months preceding their index LEA compared to individuals who remained amputation-free. Costs are presented as medians (25th–75th percentiles) expressed in 2014 euros.

		12 months preceding the index LEA		
		Diabetes Med (Q1–Q3)	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**
Index procedure	**No LEA**	€2877 (€1243–€8361) n = 15844	€1355 (€559–€4050) n = 15872	3.0 (2.86–3.15) p < 0.001
	Minor LEA	€24243 (€11952–€46516) n = 1554	€16389 (€3476–€35821) n = 758	2.39 (2.08–2.75) p < 0.001
	Major LEA	€49735 (€32315–€89455) n = 576	€37664 (€20918–€64702) n = 436	1.43 (1.13–1.82) p = 0.003
		Fold change* (95% CI) Type of intervention		
	No LEA vs minor LEA	6.21 (5.57–6.92) p < 0.001	7.79 (6.92–8.77) p < 0.001	
	No LEA vs major LEA	16.42 (13.76–19.60) p < 0.001	27.36 (23.04–32.49) p < 0.001	
	Minor LEA vs major LEA	2.65 (2.16–3.24) P < 0.001	3.51 (2.86–4.31) p < 0.001	

LEA: lower extremity amputation; Med: median; CI: confidence interval.

*Based on linear regression model with diabetes, type of intervention, age, gender and interactions. P-value after Bonferroni-Holm correction for multiple testing.

Table 2b. Median medical costs for individuals with and without diabetes undergoing minor and major LEAs during the 12 months preceding their index LEA compared to individuals who remained amputation-free, but taking into account eventual other LEA(s) in the 12 months preceding the index amputation. Costs are presented as medians (25th–75th percentiles) expressed in 2014 euros.

		Events in the 12 months preceding the index LEA								
		No LEA			**Minor LEA**			**Major LEA**		
		Diabetes Med (Q1–Q3)	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**	**Diabetes Med (Q1–Q3)**	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**	**Diabetes Med (Q1–Q3)**	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**
Index procedure	**No LEA**	€2877 (€1243–€8361) n = 15844	€1355 (€559–€4050) n = 15872	2.99 (2.85–3.14) p < 0.001						
	Minor LEA	€20673 (€10622–€37179) n = 1187	€13371 (€2674–€30659) n = 651	2.81 (2.43–3.24) p < 0.001	€39313 (€23026–€63265) n = 348	€33926 (€18163–€50473) n = 94	1.90 (1.35–2.67) p = 0.003	€89563 (€58211–€112465) n = 19	€55596 (€50016–€78032) n = 13	1.56 (0.55–4.45) p > 0.99
	Major LEA	€43835 (€26927–€68950) n = 323	€32021 (€17961–€52431) n = 322	1.79 (1.42–2.25) P < 0.001	€60367 (€37643–€98509) N = 144	€48276 (€37269–74743) n = 43	2.28 (1.37–3.78) P = 0.016	€74.014 (€41970–€116652) n = 109	€62308 (€38037–€91335) n = 71	1.40 (0.90–2.18) p = 0.96

LEA: lower extremity amputation; Med: median; CI: confidence interval.

*Based on linear regression model with diabetes, type of intervention, intervention history, age, gender and interactions. P-value after Bonferroni-Holm correction for multiple testing.

Table 3a. Median medical costs for individuals with and without diabetes undergoing minor and major LEA during the 12 months following their index LEA compared to individuals who remained amputation-free. Costs are presented as medians (25th–75th percentiles) expressed in 2014 euros.

Index Procedure	12 months following the index LEA		
	Diabetes Med (Q1–Q3)	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**
No LEA	€2284 (€852–€8323) n = 15844	€1110 (€435–€4251) n = 15872	2.54 (2.42–2.68) p < 0.001
Minor LEA	€21445 (€9989–€44142) n = 1554	€12349 (€4077–€29051) n = 758	2.04 (1.76–2.37) p < 0.001
Major LEA	€45740 (€24079–€77190) N = 576	€38666 (€18286–€66453) N = 436	1.54 (1.26–1.89) P < 0.001
	Fold change* (95% CI) Type of intervention		
No LEA vs minor LEA	8.68 (7.73–9.74) p < 0.001	10.81 (9.53–12.25) p < 0.001	
No LEA vs major LEA	22.33 (18.55–26.88) P < 0.001	36.78 (30.71–44.05) p < 0.001	
Minor LEA vs major LEA	2.59 (2.09-3.21) p<0.001	3.41 (2.75–4.22) p<0.001	

LEA: lower extremity amputation; Med: median; CI: confidence interval.

*Based on linear regression model with diabetes, type of intervention, age, gender and interactions. P-value after Bonferroni-Holm correction for multiple testing.

Table 3b. Median medical costs for individuals with and without diabetes undergoing minor and major LEA during the 12 months following their index LEA compared to individuals who remained amputation-free, taking into account eventual other LEA(s) and mortality in the 12 months following the index amputation. Costs are presented as medians (25th–75th percentiles) expressed in 2014 euros.

Index Procedure	Events in the 12 months following the index LEA								
	No LEA, one year survival			**Secondary LEA, one year survival****			**Death within year after index procedure**		
	Diabetes Med (Q1–Q3)	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**	**Diabetes Med (Q1–Q3)**	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**	**Diabetes Med (Q1–Q3)**	**No diabetes Med (Q1–Q3)**	**Fold change* (95% CI) Diabetes vs no diabetes**
No LEA	€2139 (€821–€7267) n = 15064	€1047 (€421–€3666) n = 15263	2.53 (2.41–2.66) p < 0.001				€13563 (€5852–€24948) n = 780	€13600 (€5968–€24526) n = 609	1.59 (1.34–1.90) p < 0.001
Minor LEA	€18745 (€9149–€38193) n = 1067	€9801 (€3279–€25757) n = 562	2.29 (1.95–2.69) p < 0.001	€46629 (€24870–€82639) n = 183	€44000 (€24544–€81010) n = 34	1.23 (0.70–2.17) p > 0.99	€21905 (€9566–€44281) n = 304	€17954 (€8377–€32666) n = 162	1.75 (1.30–2.36) p = 0.003
Major LEA	€54309 (€37292–€82787) n = 338	€51620 (€33356–€75778) N = 246	1.22 (0.94–1.58) p > 0.99	€92877 (€68690–€143391) n = 31	€76536 (€58356–€102638) n = 10	1.58 (0.52–4.75) p > 0.99	€20258 (€9076–€44952) n = 207	€16317 (€5903–€36540) n = 180	1.84 (1.35–2.52) p = 0.002

LEA: lower extremity amputation; Med: median; CI: confidence interval.

*Based on linear regression model with diabetes, type of intervention, events during follow-up, age, gender and interactions. P-value after Bonferroni-Holm correction for multiple testing.

**Secondary LEA: additional minor and/or major LEA(s) in the year following the index amputation.

Table 4. Fold changes in median medical costs in the 12 months following the index amputation compared to the year preceding the index amputation.

Index procedure		Diabetes	No diabetes
		Fold change* (95% CI)	**Fold change* (95% CI)**
		Cost post LEA vs cost pre LEA	**Cost post LEA vs cost pre LEA**
	Minor LEA	0.95 (0.88–1.02) p = 0.33	1.11 (0.99–1.23) p = 0.19
	Major LEA	0.84 (0.74 – 0.95) p = 0.022	0.95 (0.83 – 1.09) p = 0.48

CI: confidence interval; LEA: lower extremity amputation.

*Based on linear mixed model with diabetes, type of intervention, period (pre/post intervention), age, gender and interactions. P-value after Bonferroni-Holm correction for multiple testing.