

Travel distance to tertiary healthcare reflects disease severity and medication access in Italian Systemic Sclerosis patients: a geographical study on adult-onset rare diseases

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Additional Declarations:

Table 1 and 2 are available in the Supplementary Files section.

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ABSTRACT

Background

Systemic sclerosis (SSc) is a rare, multiorgan disease in adults that requires specialized care. Commuting to tertiary medical centers poses a considerable burden and incurs significant costs, potentially affecting management choices. This study aims to describe the healthcare commuting burden and evaluate whether longer commuting distances are associated with disease severity and differences in medication access among Italian SSc patients.

Methods

The driving distance from the city of residence to the care center was calculated using the Google Maps Distance Matrix API for patients from the Systemic Sclerosis Progression Investigation (SPRING) registry. These distances were categorized according to EUROSTAT classes. Travel distance was then correlated with clinical variables, medication access, and estimated annual pharmaceutical costs, based on standard doses and fares from the Italian Medicines Agency.

Results

The median commuting distance of the 1,795 enrolled patients was 59.4 (IQR 38.2-101.9) km, with 25.7% of them traveling more than 100 km to reach the tertiary center. Patients commuting more than 100 km to reach a tertiary center presented more frequent and severe vascular and fibrotic pulmonary complications and more commonly accessed advanced medications. The median annual drug cost was €4,407/patient, with 6.2% of patients accounting for half of the total medication budget. Drug costs reflect clinical manifestations, but correlated with commuting distances independently of disease severity.

Conclusion

Commuting distances are correlated with disease severity and the need for advanced treatments. Public health strategies should aim to enhance accessibility to specialized care and advanced therapies for these patients, recognizing the impact of travel burden on healthcare access.

KEYWORDS

Systemic sclerosis, geographical disparities, healthcare commuters, pharmaceutical costs, adult rare diseases.

BACKGROUND

Rare diseases are conditions affecting no more than 5 in 10,000 persons¹. Although most rare diseases are of genetic origin and manifest during childhood, approximately 20% are multifactorial diseases that have an adult onset, with rare inflammatory rheumatic diseases representing a significant portion. Rare diseases have peculiar care needs since patients have to often deal with the difficult to reach appropriate standards of diagnostic and treatment options, direct and indirect financial burden, and specific psychological impact².

Systemic sclerosis (SSc) is a prototypical rare adult rheumatological disease that is characterized by progressive functional impairment and potential life-threatening complications³. SSc exhibits substantial heterogeneity in terms of disease-related organ involvement and severity, with pulmonary complications, namely interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), being leading causes of mortality⁴. Due to its rarity and multi-organ nature, patients with SSc require specific clinical expertise, often within a multidisciplinary management context. SSc patients also necessitate specialized diagnostic procedures, access to specific treatments, and opportunities to participate in clinical trials. For these care needs, early referral and follow-up in tertiary medical centers are mandatory for SSc patients⁵.

In any universal healthcare system, the selection of healthcare services may be influenced by geographical factors, referral networks from primary care, and patient preferences. Commuting to reach tertiary medical centers poses a considerable burden and costs for many patients, potentially limiting access to specialized medical care⁶. The impact of commuting distance on disease severity and treatment in SSc is unknown.

This study investigates the relationship among commuting distances to healthcare tertiary centers, clinical features, and pharmaceuticals related to SSc patients in Italy, where there is a public universal healthcare system. Specifically, the study aims to evaluate whether longer commuting distances for patients are associated with different disease severity and in medication access among SSc patients receiving follow-up care at tertiary centers. Furthermore, the costs of medications were estimated for each patient and analyzed in relation to travel distances and disease characteristics.

METHODS

Study design, enrolment criteria, and variables of interest

This cross-sectional study was conducted in accordance with the STROBE (Strengthening the

Reporting of Observational Studies in Epidemiology) guidelines⁷. Eligible patients were enrolled in the SPRING registry, a multicenter non-profit national cohort study endorsed by the Italian Society of Rheumatology (SIR). The registry targeted patients with SSc and involved 38 tertiary referral hospitals⁸, distributed throughout the Italian territory.

Patients included in the analysis were enrolled between January 2018 and December 2020. They (i) had a definitive diagnosis of SSc according to the ACR/EULAR 2013 classification criteria⁹, and (ii) had available residency information. Clinical data were extracted retrospectively through a medical chart review process and administrative data¹⁰. Electronic health records were evaluated using a standardized workflow in accordance with the SPRING research protocol by clinicians directly involved in managing SSc patients. REDCap electronic data capture tools were used for data collection.

Variables of interest included demographics, comorbidities summarized within the Charlson Comorbidity Index¹¹, disease duration, anti-centromere and anti-Scl70 antibody positivity, disease domain involvement characterizing each patient, pulmonary function tests, and access to vasoactive, vasodilatory, or immunosuppressive medications.

Calculation of healthcare commuting distances

The commuting distances from the cities of residence to the tertiary care centers were calculated for anonymized patients with SSc using the Google Maps Distance Matrix Application Programming Interface. Each hospital was geolocated using Google Maps, based on the address of the corresponding Rheumatology unit as reported on the institutional website. The latitude and longitude coordinates of each residency city were obtained from the Italian National Institute of Statistics (ISTAT)¹.

Patients were categorized based on the distance traveled in a one-way trip to the healthcare center, following the European Statistical Office (EUROSTAT) guidelines on passenger mobility statistics².

According to this classification system, commuters were categorized based on different cut-offs for statistical purposes. Short-distance urban commuters traveled a one-way distance of less than 100 km and were expected by EUROSTAT system to travel within the same urban area. Other patients were classified into short-distance exurban commuters if traveled from 101 to 300 km, medium-distance commuters if traveled from 301 to 1,000 km, and long-distance commuters if traveled more than 1,001 km.

Access to medications and estimation of pharmaceutical costs

The medications used in SSc management included vasodilators (dihydropyridine calcium channel blockers, iloprost, sildenafil, tadalafil), vasoactive medications (bosentan, macitentan, ambrisentan), conventional immunosuppressants (mycophenolate mofetil, azathioprine, methotrexate), biologic immunosuppressants (rituximab, tocilizumab). Exposure to each medication was retrospectively evaluated for all patients at any disease phase as a measure of general drug access opportunities. Treatment at the time of enrollment was used for pharmaceutical cost estimates since starting and interrupting date was reported for each medication.

Annual pharmaceutical cost estimates were derived from standard dosages and costs publicly shared by the Italian Medicines Agency (AIFA)¹⁴. The least expensive available option was considered for each drug in case of expired patent. Details on the estimations of pharmaceutical costs can be found in Supplementary Table 1.

Statistical analysis

Categorical variables were reported as numbers and percentages. Continuous variables were reported as means and standard deviations (SD), or medians with interquartile ranges (IQR) (25th-75th percentiles), based on the normality of the data distribution assessed through inspection of Q-Q plots. Cross-sectional comparisons between patient groups were conducted using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney U test or t-test for continuous variables, depending on the data distribution and variance homogeneity assessed by Levene's test. Continuous variables can be log-transformed as needed to fulfill statistical test assumptions.

Logistic regression analysis was performed using 10-fold cross-validation to investigate the association of clinical variables with long commuting distance and elevated medicine costs. Variables associated with the outcome and a p-value < 0.1 were included in multivariable models with only observations without missing data included. Data were presented as Odd Ratios (OR) with 95% confidence intervals (CI).

Given that the data analyzed were derived from a registry, a formal sample size calculation was not performed. A minimum of 10 events per evaluated predictor was considered acceptable for building the multivariable regression model¹⁵.

Statistical significance was defined as a p-value less than 0.05 for all analyses, and all tests were two-tailed. A Holm-Bonferroni correction was applied in cases of multiple comparisons. Data analysis was performed using RStudio (Version 2023.12.1).

Bias Mitigation Strategies

Broad enrollment criteria were adopted and data from multiple centers were utilized to reflect a diverse demographic, geographical, and clinical representation of the SSc population in the care of tertiary centers of care. This approach aimed at mitigating selection bias and ensuring a better generalization of the findings. Data collection was standardized across centers, and clinicians with specific expertise in SSc management were involved in the chart review process to minimize information biases. In the statistical analysis, 10-fold cross-validation was used to prevent overfitting and assess how the model performs across various scenarios, thereby promoting the generalization of driven conclusions.

RESULTS

Study participants

A total of 1,849 SSc patients were enrolled in SPRING from 01/01/2018 to 31/12/2020. Fifty-four patients with missing residency data were excluded, leaving 1795 included in the final analysis. The patients resided throughout the country, particularly in proximity to the main urban centres where the enrolment sites were located (Figure 1). In particular, 504 patients resided in the North-East regions (28.0%), 403 in the North-West (22.5%), 349 from the central regions (19.4%), 414 from the South (23.1%), and 125 from the two insular regions (7.0%) of the country. Demographic and clinical characteristics of the overall population are reported in Table 1. The median commuting distance was 59.4 (IQR 38.2-101.9) km with 1,333 (74.3%) patients commuting less than 100 km and 462 (25.7%) commuting more than 100 km. Among the latter, 336 (18.7%) patients were short-distance exurban commuters, 90 (5.0%) medium-distance commuters, and 36 (2.0%) long distance commuters.

Commuting distances and their impact on clinical features in healthcare

Demographic and clinical characteristics between patients commuting more or less than 100 km are compared in Table 1. Patients commuting more than 100 km presented with ILD more frequently and had significantly lower forced vital capacity (FVC) and lung diffusion of carbon monoxide (DLco) compared to the rest of the enrolled subjects. Additionally, they presented more frequently PAH on right heart characterization and anti-Scl70 positivity and less frequently anti-centromere positivity, although the statistical significance threshold was not reached after adjustment for multiple

comparisons. Notably, there were no differences in terms of age, sex, or comorbidity burden between those two groups.

Univariate logistic regression, as reported in supplementary Table 2, confirmed and quantified the increased risk of commuting one-way distance greater than 100 km. This risk was more than doubled for patients with PAH (OR 2.38; 95% CI 1.27-3.46) and, similarly, the odds of longer commutes were also higher for ILD patients (OR 1.70; 95% CI 1.34-2.18). Anticentromere antibody positivity determined a significant reduction (OR 0.73; 95% CI 0.57-0.95) and there was also a consistent progressive increase in risk with the reduction of FVC and DLco.

Commuting distances for healthcare, access to medication and pharmaceutical expenses

Consistent with clinical heterogeneity, access to medications during disease courses summarized in Table 1 differed between commuting classes. Patients commuting less than 100 km showed lower chances of having prescriptions for iloprost, bosentan, tadalafil, cyclophosphamide, mycophenolate mofetil, and tocilizumab, with similar prescription prevalence across the two groups for all the other assessed medications.

Total estimated annual pharmaceutical costs for SSc patients were € 8,581,386 for the 38 centres, corresponding to a mean cost per patient of € 4,407/year. As expected, there was substantial heterogeneity in estimated costs, reflecting the differences in disease organ involvement. Notably, as shown in Figure 2, 1.2% of the patients required one-fourth of the total medication costs, 6.2% required half of the total medication costs, and 19.2% required two-thirds of the total medication costs of the 38 considered tertiary centres.

Given this distribution of pharmaceutical expenses, the 95th percentile was selected as the cut-off to define the subset of patients with the highest drug cost and ORs to determine higher costs calculated. In the logistic regression analysis reported in Table 2, high drug costs were associated in the univariate analysis with longer commuting distances, as well as with anti-Scl70 positivity and anti-centromere negativity, and major organ complications, mainly diffuse skin involvement, digital ulcers, ILD, and PAH. Conversely, demographics, comorbidity burden, and disease duration did not seem to affect the risk of high-cost pharmaceutical care. In the multivariate analysis, longer commuting distances were still associated with high-cost pharmaceutical care independently of all other clinical variables.

DISCUSSION

This population study quantifies the commuting burden of SSc patients and highlights how the distances to reach tertiary referral centres reflect clinical and therapeutic heterogeneity. This is the first report of this kind in SSc patients and the topic is almost completely unaddressed in adult multifactorial rare diseases.

We observed that one in four SSc patients must travel more than 100 km to access specialized healthcare, a distance that defines exurban commuters according to EUROSTAT, as it typically takes patients outside their urban area. This situation is expected to increase out-of-pocket travel costs for patients, as well as indirect costs for both patients and caregivers, in terms of lost workdays and psychological impact¹. These indirect costs are anticipated to be higher in the subgroup of exurban commuters who travel medium-long distances, defined as more than 300 km according to EUROSTAT, corresponding to 7% of the enrolled individuals. The commuting distances for patients with SSc - a rare disease with specific care needs - appear to be longer than those required to access general rheumatology evaluations derived from other populations¹⁷.

Furthermore, individuals who commute longer distances exhibit a more severe clinical phenotype, particularly in terms of interstitial and vascular lung involvement, which are the leading causes of mortality in SSc patients⁴. The study design does not allow us to directly infer the reasons for this observation. It can be hypothesized that individuals with more severe disease are more likely to choose to travel for evaluation and treatment, that referral to tertiary centers could be more likely for more complex patients, or that the physical distance from tertiary centers results in later diagnoses and less timely treatments, leading to more severe disease-related impairment. Notably, neither age nor comorbidity burden appears to be associated with different commuting distances, suggesting that these two factors do not reduce the need for individuals to seek assistance far from their residences.

Access to medications, retrospectively evaluated over the course of the disease, was also different between urban and commuters travelling more than 100 km, that had a comparable disease duration. This asymmetry reflects, at least partially, the severity of the disease and appeared more significant for second-line vasoactive or vasodilator medications such as iloprost, bosentan, and tadalafil, while was weaker for immunosuppressants, except for cyclophosphamide and tocilizumab. Possibly, a higher failure rate of first line treatment in patients with more aggressive disease that characterized in this cohort the commuters travelling more than 100 km, could also motivate the used of second-line more expensive treatments. Notably, among immunosuppressants, rituximab prescriptions appeared comparable between urban and longer travelling commuters, suggesting a widespread,

consolidated, and timely use in Italian referral centers¹⁸. Interestingly, a similar trend in the correlation between commuting distance and treatment intensity was observed in a large cohort of American patients affected by rheumatoid arthritis. The authors noted that patients who lived further from the nearest rheumatologist were more likely to receive immunosuppressants. Although the study was based solely on administrative data and did not assess disease severity, the authors suggested that unmeasured factors, such as disease severity, could influence the different treatment intensities¹⁹.

The estimated drug costs reported among SSc patients were about €4,500, which is comparable to SSc cohorts from other countries²⁰. The observed variability in the estimated pharmaceutical costs for individual patients was anticipated due to the clinical heterogeneity of SSc. However, the magnitude of this variability and its association with the commuting distance was unexpected. The cost analysis revealed that roughly 5% of patients with the most severe phenotype require half of the total pharmaceutical resources prescribed for SSc patients in Italian tertiary centers. The most severe SSc complications - namely digital ulcers, diffuse skin involvement, ILD, and PAH- are, as expected, all associated with higher pharmaceutical costs. However, commuting distance was also independently associated with higher costs, regardless of disease severity on multivariate analysis. This suggests that other variables, such as patient resources and motivation, could play a role in explaining better treatment among patients who live farther from care. This paradox, referred to as “distance bias,” has been reported in other life-threatening conditions such as cancer²¹⁻²³ but not for different conditions such as elective surgeries²⁴ or chronic diseases such as diabetes²⁵ or peripheral artery disease²⁶.

The scenario of access to care and distribution of health costs reported in this study suggests that healthcare systems should consider the distribution of healthcare costs based on the patients' actual geographical origin rather than the location of specific tertiary care reference centers for the disease, thereby allowing a more equitable distribution of national resources. This study has some limitations that must be considered when generalizing its observations. The data pertains to a national Italian SSc cohort, describing real-life scenarios within a universal healthcare system that aims to provide comprehensive health coverage to all residents in an equitable and sustainable manner. These observations may not be applicable to non-universal healthcare systems. Moreover, income and education, which are known mediators of care access and medical outcomes, were not evaluated, and pharmaceutical costs were not directly measured, but only estimated. Finally, the study might not capture the reasons behind patients' decisions to travel long distances, such as personal preferences, perceived quality of care, or previous healthcare experiences.

CONCLUSIONS

Severe SSc patients are more likely to undertake longer commuting distances and have a higher likelihood of receiving advanced and often expensive treatments. Public health strategies should aim to enhance accessibility to specialized care and advanced therapies for all SSc patients, recognizing the impact of travel burden on healthcare access. When healthcare commuting cannot be prevented, patient reimbursement should be considered. Moreover, given that SSc patients may significantly move to access care across administrative borders, healthcare costs cannot be simply attributed to the tertiary care centers but must be computed on a national scale or take into account the effective geographical origin of the patients.

LIST OF ABBREVIATIONS

AIFA	Italian Medicines Agency
CI	Confidence Interval
DLco	Lung Diffusion of Carbon Monoxide
EUROSTAT	European Statistical Office
FVC	Forced Vital Capacity
ILD	Interstitial Lung Disease
IQR	Interquartile Range
ISTAT	Italian National Institute of Statistics
OR	Odd Ratio
PAH	Pulmonary Arterial Hypertension
SIR	Italian Society of Rheumatology
SPRING	Systemic Sclerosis Progression Investigation
SD	Standard Deviation
SSc	Systemic Sclerosis
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

DECLARATIONS

Ethics approval and consent to participate

The study protocol was approved by the ethical Committees in each participating center, after the coordinating center's authorization (reference number OSS 15.010, AOU Careggi, Firenze), all patients provided written informed consent to enter in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

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Authors' contribution

Conception and design of the work: EDL, GN, MADA, RDA, CF, MMC, SLB. Statistical analysis: EDL, GN, MADA, and SLB. Acquisition, analysis, or interpretation of data: EDL, GN, RDA, LV, DG, GBaj, LD, SBR, GZ, RF, FCa, GCu, AA, ER, GL, FG, VR, EZ, IC, FI, MDS, GM, GAb, GPet, ADR, MC, AI, GCi, LB, GBag, EL, MIDA, AG, CB, MO, MF, MS, CA, GAL, MDB, EC, FL, AS, LM, CC, GDL, VC, EV, CI, GPel, EP, MGL, FFr, EG, SB, GPM, FFu, LV, SP, CLP, GBi, EF, GDB, MG, SDA, SG, FCoz, FCon, SG, AD, CS, FI, MADA, CF, MMC and SLB. Writing of initial draft: EDL, GN, MADA, RDA, CF, MMC, and SLB. Final manuscript review and approval: EDL, GN, RDA, LV, DG, GBaj, LD, SBR, GZ, RF, FCa, GCu, AA, ER, GL, FG, VR, EZ, IC, FI, MDS, GM, GAb, GPet, ADR, MC, AI, GCi, LB, GBag, EL, MIDA, AG, CB, MO, MF, MS, CA, GAL, MDB, EC, FL, AS, LM, CC, GDL, VC, EV, CI, GPel, EP, MGL, FFr, EG, SB, GPM, FFu, LV, SP, CLP, GBi, EF, GDB, MG, SDA, SG, FCoz, FCon, SG, AD, CS, FI, MADA, CF, MMC, and SLB.

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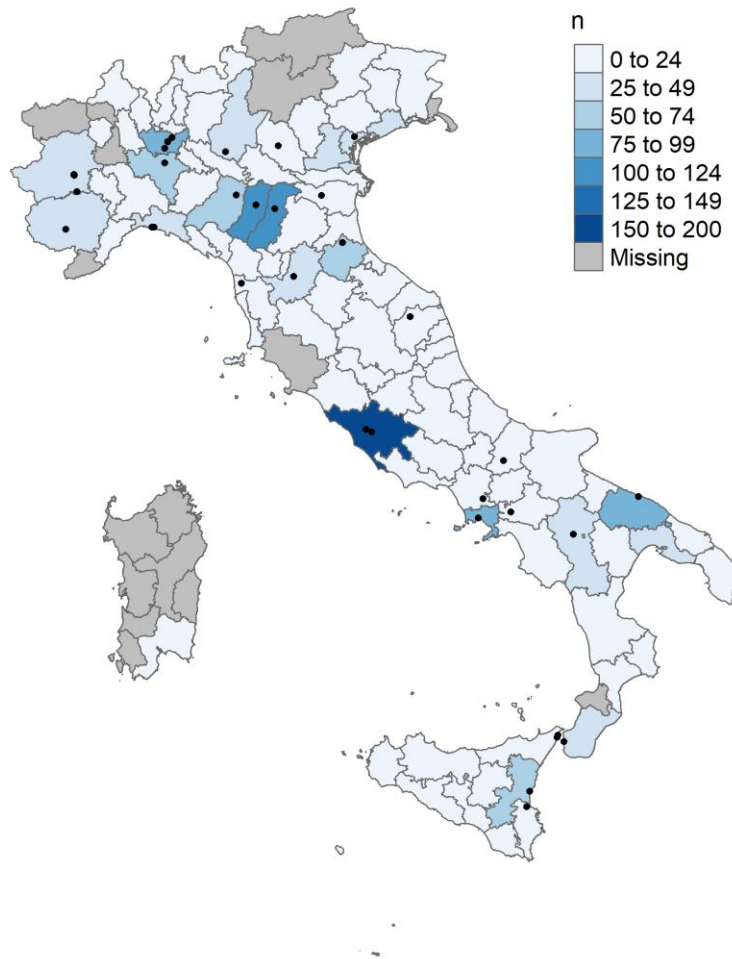


Figure 1. Geographical distribution of the residences of 1,795 study participants. *The black dots represent the enrolment sites, while the borders indicate subregional administrative divisions in Italy.*

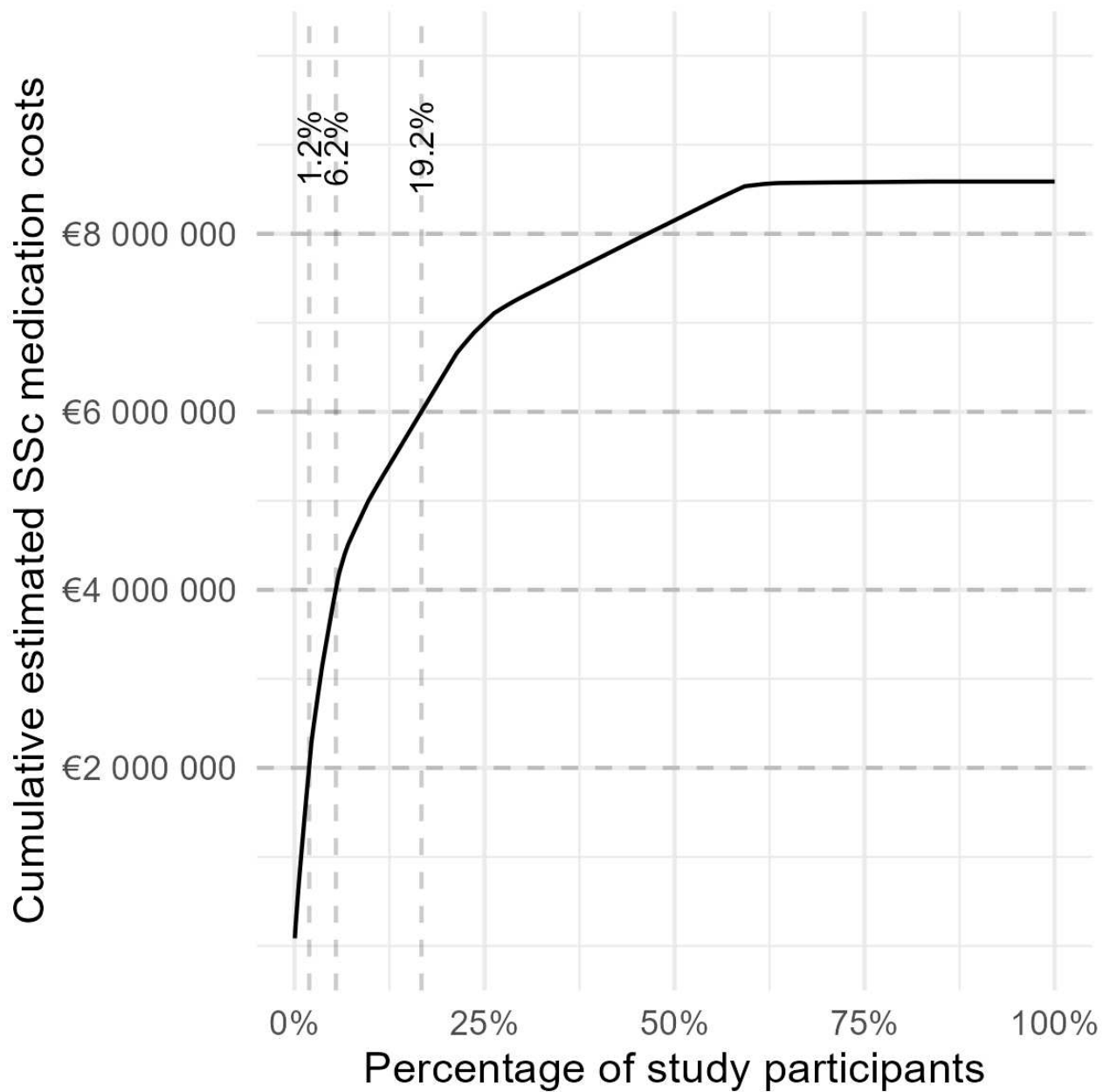


Figure 2. Cumulative Pharmaceutical Cost Plot for Decreasing Single-Patient Expenses. *Dashed lines correspond to quartiles of total drug costs.*

Supplementary Files

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