Healthcare Resource Utilization and Costs Among Patients with Essential Tremor

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Abstract

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Background: Essential tremor (ET) is a chronic neurologic movement disorder primarily characterized by an action tremor, most commonly involving the upper extremities. ET can interfere with activities of daily living, social functioning, work productivity, and health-related quality of life. Treatment options remain limited, with propranolol and primidone generally considered first-line pharmacologic therapies, though many patients do not respond to or tolerate available medications. Prior literature suggests that ET is associated with substantial clinical and economic burden; however, additional real-world evidence is needed to characterize healthcare resource utilization (HCRU) and costs attributable to ET.

Objective: To describe HCRU and quantify healthcare costs among commercially insured, Medicare and Medicaid beneficiaries with ET and compare against a cohort made up of the general population using U.S. administrative claims data.

Methods: We conducted a retrospective matched cohort study using *Merative MarketScan* databases from October 15th, 2015, through December 31st, 2024. Adults with ET were identified using ICD-10-CM diagnosis code G25.0 during the identification period. The index date was defined as the first qualifying ET diagnosis date. General population controls were sampled from the same payer databases and were assigned a random index date from a range based on the earliest and latest index dates of the ET cohort. Patients were required to have 12 months of continuous enrollment before index and were followed for 24 months after index. Patients with ET were matched on propensity scores using these variables: baseline demographics, payer type, comorbidities, pre index all-cause healthcare costs, and all-cause HCRU. All-cause costs and HCRU were examined during

the 24 months following index date, including inpatient, outpatient, emergency department, and pharmacy costs. Between group mean differences were assessed using Welch Two Sample t-tests. Costs were also evaluated using a two-part model, with a logistic regression to estimate the probability of incurring a cost, and a generalized linear model with gamma distribution and log link to estimate costs among patients with positive costs. Marginal mean differences were calculated from the two-part models, with nonparametric bootstrapping to construct 95% confidence intervals. Post-index Healthcare utilization across the different categories were evaluated using a negative binomial model and results were reported as incidence rate ratios (IRR) between ET patients and matched controls. Both regression analyses were adjusted for age, sex, insurance type, index year, and CCI.

Results: The final matched cohort included 72,343 ET patients and 72,343 matched controls from the general population. Baseline characteristics were all balanced after matching, with standardized mean differences below the prespecified threshold of 0.05. Results showed significantly higher total costs between the essential tremor and matched general population cohorts with a mean difference of $5,747.22 (95% CI: 4,610 – 6,875, p<0.001). A two-part model with additional regression components also showed significantly higher total costs between the essential tremor and general population cohorts with a mean difference of $9,927.92 (95% CI: 8797.56 – 11,019.98, p<0.001). Due to the difference between these two results, additional models were run as a sensitivity analysis and showed a range of mean differences from $5,995.32 to $9,373. All models were directionally consistent and showed ET being associated with higher total costs compared to the general population. Costs were primarily driven by outpatient services, and secondarily by pharmacy costs. During the post-index follow-up period, ET patients were found to have higher (incidence rate ratio [IRR] = 1.32, p < 0.001) overall utilization compared with matched controls. Rates of inpatient encounters (IRR = 1.42, p < 0.001) and emergency department encounters (IRR = 1.47, p = < 0.001) were also both found to be significantly higher among ET patients. Outpatient encounter rates were also found to be higher (IRR = 1.31, p = < 0.001) among ET patients.

Discussion: Adults with ET experienced greater HCRU and costs compared with the general population, as shown by increased healthcare costs and higher rates of total encounters in every setting. These findings highlight the real-world economic burden associated with ET and call for the need for future evaluations of disease management strategies and emerging therapies.

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1. Introduction

Essential tremor (ET) is one of the most common movement disorders, affecting an estimated ~7 million people in the U.S., or ~2.2% of the population, with prevalence increasing substantially with age [1,2]. It is a chronic neurologic movement disorder most characterized by bilateral upper-limb action tremor. Tremor symptoms can interfere with writing, eating, drinking, dressing, and other activities of daily living, contributing to functional limitations, embarrassment, and reduced quality of life [5, 6]. In addition to motor symptoms, ET may be associated with non-motor manifestations, including mood, sleep, and cognitive symptoms, which may further contribute to disease burden [7]. Despite its frequency, ET may be under-recognized or inconsistently treated, creating challenges for estimating its full clinical and economic burden [8].

Pharmacologic treatment options for ET remain limited as management of ET is primarily symptomatic, and not curative or disease-modifying. Propranolol and primidone are commonly considered first-line options [9,10], but 30% to 50% of all patients do not respond to or tolerate these therapies [11]. Other evidence also suggests that discontinuation rates for propranolol and primidone can range from 10% to as high as 70% [24]. For patients with medication-refractory tremors, procedural therapies such as deep brain stimulation and focused ultrasound may be an option, but these approaches are not appropriate for all patients and can be considered invasive procedures [11]. Although they can be an effective at symptom improvement, they also involve substantial treatment costs ranging from $31,810–$74,721 for deep brain stimulation [20] and $19,000–$25,000 for focused ultrasound [21]. Inadequate symptom control may leave patients with persistent functional limitations that require continued medication management, and management of tremor-related consequences. One of which may be increased gait and balance impairment as studies have reported that ET patients have greater fall risks [22, 23]. These limited existing treatment options may contribute to persistent disease burden and continued HCRU and costs through ongoing symptom management, fall-related or functional complications, and high-cost procedures.

Psychological comorbidities such as anxiety, depression, and alcohol use disorder have higher prevalence in ET patients, which may further increase healthcare utilization [12,13]. In addition to direct healthcare costs, indirect costs such as work absenteeism and disability are underrepresented in the existing literature on ET, resulting in an incomplete understanding of the full societal impact of the disease [14]. Despite the high prevalence of ET,

data characterizing all-cause healthcare resource utilization (HCRU) remains limited, particularly in real-world settings.

Prior real-world studies have begun to characterize ET-associated comorbidities, psychiatric conditions, healthcare utilization, treatment patterns, and costs. Dai et al. [12] found that ET patients had higher rates of inpatient admissions (21.0% vs. 16.5%), emergency department visits (30.2% vs. 25.0%), and mean total healthcare costs ($17,560 vs. $13,237). They also found ET to have a higher comorbidity burden, including greater prevalence of depression (25.6% vs. 15.3%) and anxiety (27.7% vs. 15.5%). Pahwa et al. [13] similarly found higher HCRU and costs among ET patients over 24 months, with mean total costs of $36,241 compared to $13,780 among non-ET patients. They also found evidence that cost burden appeared to increase with ET medication use, suggesting greater resource use among patients requiring more intensive pharmacologic management. Another analysis by Louis et al. found that adults with ET aged 40 years or older had annual direct medical costs of $28,217 which was $1,601 higher than their matched comparison [16]. Together, these studies suggest that ET patients may experience higher healthcare utilization and costs compared with non-ET patients, and that the burden may increase with medication use or comorbidity complexity.

Prior real-world studies have contributed important evidence on the economic burden of ET, however, aspects of these studies limit how fully their findings characterize the disease. To our knowledge, prior studies have focused on commercially and Medicare insured populations and have missed important populations such as Medicaid-insured ET patients [12, 13, 16]. Medicaid covers a clinically and demographically distinct group made up from those qualifying through disability, dual-eligible beneficiaries, and lower-income enrollees whose comorbidity profile, reimbursement rates, and access to specialty and procedural care differ from those captured in commercial and Medicare data. Another key aspect lies in their matching design. Pahwa et al. solely reports its outcomes using unadjusted, descriptive differences with no statistical analysis, reflecting potential residual confounding due to baseline health status and comorbidity burden and leading to overestimated cost differences. Dai et al. also opted not to match on baseline spending and utilization which could weaken their between group comparisons and overestimate the reported post diagnosis cost increases. In contrast to those studies, our study improves on these approaches by capturing Medicaid beneficiaries alongside the commercially insured and Medicare Supplemental populations, using a matched general population comparator cohort, and accounting for baseline healthcare spending and utilization. These aspects allow for a more

comprehensive estimate of the HCRU and cost burden associated with ET while allowing for greater external validity, increasing generalizability, and capturing a more nationally representative population.

The primary objective of this study is to quantify healthcare resource utilization among commercially insured, and Medicare Supplemental and Medicaid beneficiaries with essential tremor. ET patients will be compared to a control group made from a matched sample from the general population to evaluate the inpatient, outpatient, and pharmaceutical costs of essential tremor.

2. Methods

2.1 Study Design and Data Source

This retrospective cohort study used the Merative MarketScan Commercial Claims and Encounters, Medicare Supplemental, and Medicaid claims databases which capture healthcare claims data for over 273 million insured individuals in the United States. These databases contain de-identified enrollment information and adjudicated inpatient, outpatient, and pharmacy claims. The study period began on October 15th, 2015, to align with the availability of ICD-10-CM diagnosis coding and ended on December 31st, 2024. Because this study used de-identified claims data, it was considered exempt from institutional review board review.

2.2 Study Timeline

The baseline period was defined as the 12 months before index. The follow-up period extended from the index date through 24 months after index. The index date for ET patients was defined as the first ET (G25.0) outpatient diagnosis claim. General population controls were assigned an index date by randomly selecting a date between the earliest and latest ET index dates. Controls were required to meet the same baseline and follow-up enrollment requirements as ET patients. The assigned index year will be used in Propensity Score Matching as outlined in *Section 2.6*.

2.3 Study Population

Patients were identified separately by payer (Commercial, Medicare, Medicaid) dataset and then combined for the final analytic dataset after cohort construction and matching.

2.3.1 Cohort Selection

Patients with ET were identified using ICD-10-CM diagnosis code G25.0. The ET case definition required at least one outpatient claim with a diagnosis code for ET. Eligible patients were required to meet the following criteria: (1) Age ≥18 years on index date, (2) continuous enrollment for 12 months before index to establish baseline characteristics, establish baseline comorbidity scores, and quantify pre-index costs and utilization. (3) Continuous enrollment for 24 months post-index was also required to provide sufficient time to track post-index healthcare utilization and costs. Patients were excluded from the ET cohort if they had ≥1 claim with a diagnosis code for Parkinson's disease (G20.0) anywhere in the study period. This was done to reduce diagnostic misclassification as the two conditions have many overlapping symptoms and have high misdiagnosis rates [25]. Excluding these patients helped ensure that the observed healthcare burden was more likely attributable to ET rather than Parkinson's or mixed tremor syndrome. Patients were also excluded if they were missing entries for age or sex sexduring the 12-month pre-index baseline period as they were critical for matching.

General population controls were randomly sampled from eligible enrollees from the same MarketScan payer databases as the ET cohort. The initial control cohort was comprised of a simple random selection of 100,000 unique individuals per study year, from each of the 3 payer databases, totaling 3,000,000 individuals. Controls were required to have no qualifying ET diagnosis or Parkinson's disease diagnosis during the study period and were also required to meet the same age and continuous enrollment requirements as ET patients. Controls were assigned a random index date from a range based on the earliest and latest index dates of the ET cohort. Baseline characteristics were measured relative to that assigned index date.

2.4 Baseline Characteristics

Baseline characteristics were assessed during the 12-month pre-index period. Demographic variables included age, sex (female/male), and payer type (Commercial, Medicare, Medicaid). Also included was the index year, Charlson comorbidity index (CCI), and rates of common comorbidities listed in *Table 1* and *Appendix B*. The CCI was calculated using the comorbidity package in R which collects ICD-10 codes from diagnosis claims collected during the 12-month pre-index period. The score was age-adjusted using a standard scale of additional points given based on patient age according to the following categories: 50-59 (+1), 60-69 (+2), 70-79 (+3), and ≥80 (+4).

2.5 Outcomes

Healthcare resource utilization and all-cause healthcare costs were measured during both the pre-index and post-index periods. Outcomes were assessed overall and by encounter setting.

2.5.1 Healthcare Resource Utilization

HCRU outcomes included inpatient admissions, emergency department visits, and outpatient visits. Unique encounter counts were calculated separately for the 12-month pre-index and 24-month post-index periods to characterize healthcare contact before and after the index date. Utilization was categorized into Inpatient, Outpatient, and Emergency Department (ED) visits using a combination of variables that indicate the place of service for that claim. The exact schema used for categorization is listed in *Appendix D*.

2.5.2 Healthcare Costs

Healthcare costs were calculated using the sum of direct payments on adjudicated claims. These payments included insurer and health plan payments, as well as patient cost-sharing through copayments, deductibles, and coinsurance. Cost outcomes were divided into category-specific costs for inpatient, outpatient, emergency department, and outpatient pharmacy claims. Costs were summarized over the 12-month pre-index period and 24-month post-index follow-up period.

2.6 Propensity Score Matching

Propensity score matching was used to reduce confounding due to observed baseline differences between ET patients and general population controls. Propensity scores were estimated using logistic regression, with ET status as the dependent variable. Matching covariates included age, sex, region, payer type, index year, pre-index total healthcare costs, pre-index healthcare utilization, and age-adjusted comorbidity score as well as a set of common comorbidities found in *Table 1* and *Appendix B*. Matching was performed using nearest neighbor without replacement and using a 1:1 matching ratio. The average treatment effect on the treated (ATT) was targeted to focus on the effects of ET in these patients and isolate their excess costs and HCRU, so that it can be compared to a baseline made from the matched general population cohort. Covariate balance was assessed using standardized mean differences, with values ≤0.05 considered indicative of acceptable balance.

2.7 Statistical Analysis

For the primary objective to characterize and quantify healthcare costs and utilization of ET, patients were evaluated 24 months after their ET diagnosis to see whether they had higher average costs and utilization compared to matched patients from the general population.

2.7.1 Cost Analysis

Costs were summarized cumulatively over the 24-month follow-up period and mean costs were compared between ET patients and matched controls overall and by place of service category. Costs were summarized descriptively using means, standard deviations, medians, and interquartile ranges, and the between group mean differences were assessed using Welch Two Sample t-tests.

Due to the overall right-skewed distribution of the cost data and disproportionate number of zero values in the Inpatient and ED cost categories shown in Table 6.4.7 and Figure E.1, between-group differences were also evaluated using a two-part regression model where a logit regression model was first used to assess the likelihood of having any healthcare expenditures. For the second part, a generalized linear model with gamma distribution and log link was used to evaluate the association between healthcare expenditures and essential tremor among those who had non-zero costs. Both parts of the two-part model were adjusted for age, sex, insurance type, index year, and CCI. The covariates used are summarized in *Section 6.4's* tables, along with the estimated coefficients from both parts of the model. The recycled predictions method was used to estimate the increment (average marginal effect (AME)), in average total spending for each cost category between the essential tremor and matched general population cohort [30]. A bootstrap function was wrapped around the two-part model, and using R's *boot* package, 1,000 non-parametric bootstrapping iterations were run on the function to generate a 95% confidence interval around the AME.

2.7.2 Healthcare Utilization Analysis

Post-index HCRU was compared between ET patients and matched controls. For encounter count outcomes, including number of inpatient admissions, outpatient encounters, and pharmacy claims, groups were compared using negative binomial regression due to it being better suited for data with overdispersion. This model was also adjusted using age, sex, insurance type, index year, and CCI and the covariates along with the estimated coefficients are summarized in *Section 6.5's* tables. The AME was calculated using the *marginaleffects* R package. A bootstrap function was wrapped around the negative binomial model, and using R's *boot* package,

1,000 non-parametric bootstrapping iterations were run on the function to generate a 95% confidence interval around the AME.

2.7.3 Software

Data extraction and management, and cohort selection were all conducted using SAS version 9.4 and R version 4.6.0. Propensity Score Matching was performed using the *MatchIt* package, and covariate balance was assessed using the cobalt package. All statistical analysis was performed using R version 4.6.0.

3. Results

3.1 Cohort Selection and Attrition

A total of 244,231 patients had at least one claim with an ET diagnosis code during the study identification period. After applying the continuous enrollment restrictions, 75,805 patients remained. Following exclusion of patients younger than 18 years, those with insufficient baseline enrollment, missing demographic information, or other exclusion criteria, the final eligible ET cohort included 72,343 patients. The ET and general population cohorts' attrition is diagramed in Figure 2.1 and 2.2. After applying all inclusion and exclusion criteria, the eligible general population control pool included 276,885 patients before matching. After propensity score matching, the final analytic cohort included 72,343 ET patients and 72,343 matched controls.

3.2 Baseline Characteristics Before and After Matching

Baseline characteristics after propensity score matching are summarized in *Table 1* and before matching in *Appendix A*. Before matching, the eligible ET cohort included 72,343 patients and the eligible general population control cohort included 276,885 patients. Patients with ET were older on average than patients in the general population cohort, with a mean age of 58.7 years compared to 53.3 years of age. The distribution of sex was generally similar before matching, with females representing 56.1% of the ET cohort and 57.9% of the general population cohort.

Before matching, the distribution of payer type differed between cohorts. A greater proportion of ET patients were commercially insured compared with general population controls (45.9% vs. 30.0%), while a smaller proportion were Medicare beneficiaries (21.2% vs. 34.2%). Medicaid beneficiaries represented 32.9% of the ET cohort and 35.8% of the general population cohort.

After 1:1 propensity score matching, the final analytic cohort included 72,343 ET patients and 72,343 matched general population controls. Matching substantially improved balance across measured baseline characteristics and all matched covariates were within the prespecified balance threshold of 0.05. Covariate balance before and after matching is further illustrated in *Figure 3*.

3.3 Post-Index All-Cause Healthcare Costs

Patients with ET incurred higher mean total healthcare costs compared with matched general population controls. Mean total post-index costs were $35,924.58 among ET patients compared with $30,177.36 among matched controls, corresponding to a mean difference of $5,747.22 (95% CI: $4,610 to $6,875; $p < 0.001$). Category-specific cost differences were observed across all encounter settings and are summarized in *Table 6.2*. Pharmacy costs accounted for the largest incremental difference between cohorts, with ET patients incurring $1,961 higher costs than matched controls. Inpatient costs were also higher among ET patients, with an estimated difference of $1,625, followed by outpatient costs $1,590 and emergency department costs $571.

Average all-cause costs over the 24-month follow-up period for both the ET and matched general population cohort are shown in *Figure 4*. Among ET patients, outpatient services represented the largest component of total healthcare costs, followed by inpatient services, pharmacy claims, and emergency department services. Mean 2-year outpatient costs after ET diagnosis were $16,039 among ET patients compared with $14,449 among matched controls. Mean inpatient costs were $9,805 among ET patients and $8,180 among matched controls. Mean pharmacy costs were $7,945 among ET patients compared with $5,983 among matched controls. Mean emergency department costs were $2,135 among ET patients and $1,563 among matched controls. Overall, ET patients had higher average costs across every measured cost category during the 24-month follow-up period.

The difference in average all-cause costs between the ET and matched general population for each cost category are further broken down by decile and shown in *Figure 5*. From the figure, we can see that the last decile of individuals with essential tremor and in the general population represent a very significant portion of the overall healthcare spending across each cost category. This further demonstrates how the average post index costs of both cohorts are highly right skewed in addition, the largest differences in mean costs between the ET and general population cohorts were also found in the last decile.

Adjusted healthcare costs estimated from the Two-Part model were reported across all cost categories in *Table 6.4.6* as the average treatment effect on the treated (ATT). Total post index healthcare costs for the essential tremor cohort were estimated to be $9,927.92 (95%: 8797.56, 11,019.98) higher than general population controls. When comparing the ATT across categories, ET outpatient costs remained the largest incremental category with an estimated difference of $3,706 (95%: 3,238.70, 4,208.86), followed by pharmacy prescription costs with an estimated difference of $2,771.02 (95% CI: 2,366.20, 3,248.70) over the general population cohort. Inpatient ($1,896.44; 95% CI: 1,204.81, 2,463.65) and Emergency department (609.21; 95% CI: 540.11, 677.49) costs also showed higher estimated costs for ET after adjustment. *Section 6.4* summarizes the covariates used in the two-part models for adjusting healthcare costs and their estimated coefficients. Overall, the results from the logit model indicate that having an ET diagnosis is associated with an increase in probability of having at least some cost across each setting, and that among those who do have costs, the Gamma model indicates an increase in spending overall, as well as in outpatient, ED, and pharmacy specific costs.

Due to the difference between the cost results of the Matched ATT and the ATT predicted by the Two-Part Model, we suspect that the chosen two-part model may have had a hard time capturing an appropriate cost model. A Modified Park test [29] was carried out to evaluate if the chosen Gamma family for part two of the model was appropriate and resulted in a lambda of 1.74, suggesting that the Gamma distribution may be a reasonable choice. To evaluate the chosen log link, a Pregibon link test [31] was conducted and was shown to be significant, indicating that the link function may be incorrectly specified for the second part of the two-part model. For further evaluation, a sensitivity analysis was carried out where additional regression models were implemented. Model families chosen were OLS, Log Normal, Gamma Identity, and Tweedie. The analysis was focused on total costs and outpatient costs as these two categories showed the greatest divergence between the two ATT estimates. Across all the models, a range of mean differences in total costs from $5,995.32 to $9,373 was estimated. The mean difference in outpatient costs estimated by the models ranged from $1,718.67 to $3,845.33. The Gamma identity failed for both outcomes due to it generating negative predicted values. The Log Normal estimated a mean difference $6,519.81 for total costs and $2,630.48 for outpatient costs. Across the specified variance parameters in *Table 6.8.2*, the Tweedie family models estimated a range of mean differences from $6,546 to $9,373 for total costs and $1,973 to $3,366 for outpatient costs. The OLS model produced values most consistent with the ATT result from the matched cohorts with a mean difference in total costs of $5,995.32 and $1,718.67 for outpatient costs. Initial matching balance was strong and the additional

regression factors from the OLS did not have a large effect on the predicted ATT, suggesting that the more complex models had a harder time fitting a model and may be overestimating the difference in costs. Despite the range of values produced, all models were directionally consistent and showed ET being associated with higher costs compared to the general population. Estimates of our primary outcome of mean difference in total post index costs fell between $5,747.22 and $9,927, with inpatient costs between $1,625.04 and $1,869.44, outpatient costs between $1,590.27 and $3,706.73, emergency department costs between $571.66 and $609.21, and pharmacy prescription costs between $1,961.24 and $2,771.02.

3.4 Post-Index All-Cause Healthcare Resource Utilization

Patients with ET had higher overall healthcare utilization compared with matched general population controls. The mean number of total encounters between the matched ET and general population cohort was 67.6 among ET patients compared with 59.0 among matched controls, corresponding to a mean difference of 8.6 encounters (95% CI: 7.322 to 9.864; p < 0.001). As summarized in *Table 6.3*, the majority of encounters were, on average, seen in the outpatient setting for both the ET and general population cohorts with an average of 65.2 and 57.2, respectively, for a mean difference of 8.0. Higher average utilization was also observed for Inpatient admissions (0.4 vs 0.3), and Emergency Department visits (2.0 vs 1.4).

Negative binomial regression results for post-index healthcare resource utilization were reported in *Table 6.6* as incidence rate ratios (IRR) and the covariates used in the regression and their coefficients are summarized in *Section 6.5*. Patients with ET had significantly higher total encounter rates than matched controls (IRR = 1.32; 95% CI: 1.30-1.33; p <0.001). Utilization was also significantly higher across each care setting. ET patients had higher inpatient admission rates (IRR = 1.42; 95% CI: 1.38-1.45; p <0.001), higher outpatient visit rates (IRR = 1.31; 95% CI: 1.30-1.33; p <0.001), and higher emergency department visit rates (IRR = 1.47; 95% CI: 1.44-1.49; p <0.001). These findings indicate that ET was associated with greater all-cause healthcare utilization during follow-up, with the largest relative increases observed for emergency department visits and inpatient admissions.

Based on the adjusted negative binomial model results summarized in *Table 6.7*, the average marginal effects of ET were associated with significantly greater post-index healthcare utilization across all encounter categories. On average, patients with ET were estimated to have 17.66 (95% CI: 16.96, 18.37) additional total encounters when compared with the matched general population cohort. This difference was driven primarily by outpatient

utilization, with ET being associated with 16.83 (95% CI: 16.13, 17.52) more outpatient visits. Smaller average increases were also observed for inpatient admissions (0.135; 95% CI: 0.125, 0.144) and ED visits (0.670; 95% CI: 0.639, 0.701). Similar to the cost outcomes, differences were observed between the mean total and outpatient encounter results produced by the matched cohorts and the predicted values from the negative binomial regression model, suggesting that a similar issue affects the negative binomial regression. Estimates of our primary outcome of mean difference in total post index healthcare utilization between the ET and general population fell between 8.6 and 17.7, with inpatient admissions between 0.1 and 0.14, outpatient visits between 8.0 and 16.8, and emergency department encounters between 0.6 and 0.67.

4. Discussion

In this study, patients with essential tremor were found to have higher costs across every measured category, including inpatient, outpatient, emergency department, and pharmacy costs, suggesting that the economic burden associated with ET is distributed across multiple parts of the healthcare system rather than concentrated in any one setting. These results are also consistent with prior real-world studies showing that ET is associated with increased healthcare utilization and healthcare costs when compared with non-ET populations [12-16].

From our primary analyses, ET was shown to be associated with $5,747.22 to $9,927 higher total healthcare costs over the 24-month follow-up compared with the general population. This result suggests that ET is associated with greater economic burden even after adjusting for patient age and sex, their insurance type, and comorbidity burden. Dai et al. reported a 12-month cost difference of $4,323 between ET and non-ET patients, compared to our upper bound annualized estimate of approximately $4,963 per year, making the estimates relatively similar. Pahwa et al. reported a larger $22,461 mean cost difference in commercial patients and $19,152 in Medicare patients across a 24 month follow up period. While both prior studies and ours both show ET-associated increases in healthcare costs, the difference in the magnitude of our cost results may be reflected in some of our methodological differences. Pahwa did not employ a matched cohort comparison and solely reported unadjusted descriptive results meaning their reported results may be overestimated. Dai et al. matched on demographics and insurance type, similarly to our study, but not on comorbidities, baseline costs, or baseline utilization. Matching on the pre-index costs and utilization reduced the magnitude of our study's mean difference between the matched ET and general population cohorts down from $13,690.89. However, it allows for the ET and general population cohorts to have a more comparable baseline health status and

strengthens our between group comparisons. Also, the inclusion of Medicaid into our study population adds a unique patient population mix with their own healthcare spending and utilization patterns that are not accounted for in the other studies.

Pharmacy costs showed the largest category-specific cost difference between ET patients and matched controls, with ET patients incurring $1,961 higher pharmacy costs over 24 months. Although propranolol and primidone may account for some of these costs, they are generally inexpensive medications. This difference may reflect broader medication use among ET patients, including the addition of second and third-line therapies, and the treatment of comorbid conditions and their adverse effects. This aligns with prior evidence reported by Pahwa et al. that found that total healthcare costs increased as the number of ET medications increased and were highest among commercially insured patients receiving two ET medications and among Medicare patients receiving three or more ET medications [13]. These increased pharmacy costs for ET patients reflect the difficulty of overall disease management caused by polypharmacy and the limited availability of effective treatment options.

The largest relative increases in utilization were observed for emergency department visits and inpatient admissions. ET patients had 47% higher ED visit rates and 42% higher inpatient admission rates than matched controls. This suggests that ET patients may have greater acute healthcare needs, not only greater routine outpatient care. These results are reflective of the higher overall comorbidity burden found by prior claims-based studies. Dai et al. found that the presence of psychiatric disorders such as anxiety, depression, and substance abuse disorders were associated with increased healthcare costs and concluded that they were major drivers of the increase in costs that these patients face [12]. Pahwa et al. found similar results and reported that ET patients faced higher rates of those same psychiatric comorbidities [13]. They also found higher rates of falls, which align with the and the reported increase in fall risks and functional impairments related to tremor and balance problems [22, 23]. Together, these findings suggest that ET may be associated with broader healthcare burden beyond routine tremor management alone.

4.1 Limitations

This study has several limitations, some of which are inherent to any retrospective, claims-based analysis. Firstly, ET was identified using ICD-10-CM diagnosis code G25.0 in administrative claims data. Claims-based case definitions may be subject to diagnostic misclassification, coding errors, or incomplete capture of disease

status. ET may also be underdiagnosed or misdiagnosed in routine clinical practice, which is hard to identify through claims with certainty and thus could affect cohort identification. Secondly, although propensity score matching achieved balance across measured baseline characteristics, residual confounding may remain due to unmeasured factors not available in claims data, such as tremor severity. Claims data also do not capture clinical measures such as tremor rating scales, or patient-reported outcomes. This makes it difficult to stratify essential tremor patients by disease severity which introduces potential issues with generalizability as without this data we may be only estimating the effects of the more severe, care-seeking ET patients. Patients with a milder burden of ET may never even seek care or receive a diagnosis code, leaving those with more severe cases who are more likely to seek more extensive care, overrepresented in our study population. This combination could potentially lead to an overestimation of our cost and utilization results, making the disease appear more costly than it would when compared to the entire ET population, especially if severity is significant driver of healthcare costs.

Anxiety, depression, and alcohol use disorder were not included as matching covariates in the final analysis because each may be associated with ET. Prior studies have reported higher prevalence of anxiety, depression, substance use disorders, or alcohol abuse among patients with ET compared with non-ET controls [12,17]. Matching on these conditions could potentially adjust away part of the burden associated with ET if they represent downstream manifestations or consequences of the disease; however, not matching on these variables may also leave residual confounding and affect healthcare utilization and costs. Future analysis of the impact that these comorbidities have on ET patients may help clarify whether ET is driven more by the tremor-related care, or if these comorbidities independently contribute to the observed increases in costs and utilization.

Requiring 24 months of continuous enrollment ensured complete observation of healthcare resource utilization and costs but had a significant reduction in the ET cohort size from 244,431 to 75,805, as shown in *Figure 2.1*, and excluded patients who disenrolled, changed insurance coverage, died, or otherwise left the database during the follow-up period. Since ET is a chronic and progressive disorder, the fixed 24-month follow-up may not fully capture costs associated with care that emerges later as a patient's tremor worsens and functional impairment increases. Patients requiring specialist care or advanced therapies like deep brain stimulation or focused ultrasound could also potentially be underrepresented as these are usually undergone by more severe patients in the later stages of progression. Due to the length of time needed, these individuals may not be fully captured in our follow-up period. As a result, our study's results may underestimate the longer-term economic burden of

ET. An alternative approach to recover the patients lost to the enrollment window would be to follow all patients from index until the earliest of either disenrollment, end of data availability, or the end of the planned study period, but this would introduce right censoring due to the variable follow up time between individuals. To account for the right censoring, future research would use a method such as inverse probability of censoring weighting [26-28] to recapture patients lost to follow-up, allowing them to still contribute to the final cohort.

An additional limitation is that the estimated outcomes for both healthcare costs and healthcare utilization differed between the matched mean differences and the model-based average marginal effects. As Basu and Rathouz [30] describe, generalized linear models (GLMs) with the correct specifications can correspond to the underlying distribution of an outcome measure, however, they are not universally correct. Model-based estimation of marginal or incremental effects should not rely on any one generalized linear model specification when the appropriate link and variance are uncertain. Even when a linear model is correct, resulting estimators could be unstable, due to skewness, kurtosis, or heteroscedasticity. Therefore, future work would systematically explore other model specifications for both the cost outcome and utilization outcome measures using the framework proposed by Basu and Rathouz [30] and estimate parameters for the link and variance functions along with the linear predictor to guide selection for the best regression model.

5. Conclusion

In this study, findings show that patients with essential tremor had significantly higher all-cause healthcare resource utilization and healthcare costs compared with matched general population controls during the 24-month follow-up period. They experienced higher total encounter rates and greater utilization across inpatient, outpatient, and emergency department settings. They also incurred higher total healthcare costs, with cost differences observed across inpatient, outpatient, emergency department settings as well as pharmacy prescription costs. These findings demonstrate that essential tremor is associated with substantial real-world healthcare burden and support the need for improved disease management strategies, additional treatment options, and further research into the clinical and economic impact across the different payer populations.

6. Tables and Figures

Table 6.1: Baseline Characteristics* of Matched ET and General Population Cohort – After Matching

	ET n = 72,343	General Population n = 72,343	SMD†
Age			
Mean (SD†)	58.7 (16.0)	58.9 (16.4)	0.0129
Median (IQR†)	59.0 (50.0, 70.0)	58.0 (49.0, 71.0)	
Range (Min – Max)	18.0 – 105.0	18.0 – 102.0	
Sex, %			
Male	43.9%	43.8%	<0.001
Female	56.1%	56.2%	<0.001
Insurance Plan type, %			
Commercial	45.9%	44.8%	0.0113
Medicare	21.2%	22.6%	0.0145
Medicaid	32.9%	32.6%	0.0032
Index Year, %			
2015	11.8%	10.8%	0.0099
2016	22.7%	23.3%	0.0064
2017	14.9%	15.3%	0.0041
2018	10.7%	10.8%	0.0011
2019	11.8%	11.9%	0.0015
2020	9.2%	9.1%	0.0015
2021	9.9%	9.8%	0.0018
2022	8.1%	8.1%	<0.001
2023	0.9%	0.9%	<0.001
Charlson Comorbidity Index (CCI)			
Mean (SD†)	2.8 (2.5)	2.9 (2.6)	0.0123
Median (IQR†)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	
Range (Min – Max)	0.0 – 21.0	0.0 – 21.0	
Comorbidities, %			
COPD†	20.8%	20.7%	0.0011
Congestive Heart Failure	6.3%	6.3%	<0.001
Diabetes	11.8%	12.3%	0.0046
Peripheral Vascular Disease	8.0%	8.2%	0.0021
Cerebrovascular Disease	8.3%	8.0%	0.0029
Renal Disease	6.7%	6.9%	0.0020

Liver Disease	4.8%	4.9%	0.0018
Malignancy	5.6%	5.8%	0.0021
Rheumatoid Disease	3.1%	3.0%	<0.001
Total All-Cause Pre-Index Costs ($)			
Mean (SD†)	15,421.69 (41,963.80)	15,039.16 (56,849.75)	0.0091
Median (IQR†)	4,618.57 (1,168.88, 14,521.24)	2,785.84 (560.81, 11,075.79)	
Range (Min – Max)	0.00 – 2,639,997.30	0 – 3,450,928.15	
Total All-Cause Pre-Index Encounters, n			
Mean (SD)	31.6 (54.7)	30.1 (64.3)	0.0281
Median (IQR)	16.0 (7.0, 32.0)	11.0 (4.0, 25.0)	
Range (Min – Max)	0.0– 414.0	0.0 – 422.0	

** Baseline characteristics: Covariates used in matching that were collected during 12-month pre-index period.*
† SD: Standard Deviation; IQR: Interquartile Range; SMD: Standardized Mean Difference; COPD: Chronic Obstructive Pulmonary Disease

Table 6.2: All-Cause Healthcare Costs for the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

Outcome	ET Mean (SD)	General Population Mean (SD)	Mean Difference (95% CI)	p-value
Total costs	35,924.58 (118,649.80)	30,177.36 (101,195.87)	5,747.22 (4,610.00 – 6,875.00)	< 0.001
Inpatient costs	9,805.37 (85,182.11)	8,180.33 (54,978.97)	1,625.04 (940.00 – 2,432.00)	< 0.001
Outpatient costs	16,039.66 (45,388.01)	14,449.39 (66,877.85)	1590.27 (985.00 – 2198.00)	< 0.001
ED costs	2,135.39 (7,020.13)	1,563.73 (6,518.55)	571.66 (494.20 – 640.70)	< 0.001
Pharmacy costs	7,945.15 (48,320.65)	5,983.91 (32,036.76)	1961.24 (1,548.00 – 2,429.00	< 0.001

Table 6.3: All-cause Healthcare Resource Utilization for the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

Outcome	ET Mean (SD)	General Population Mean (SD)	Mean Difference (95% CI)	p-value
Total encounters	67.6 (108.9)	59.0 (122.8)	8.6 (7.3, 9.9)	< 0.001
Inpatient admissions	0.4 (1.1)	0.3 (1.0)	0.1 (0.1 – 0.1)	< 0.001
Outpatient visits	65.2 (107.5)	57.2 (121.8)	8.0 (6.7 – 9.2)	< 0.001
ED visits	2.0 (4.4)	1.4 (5.2)	0.6 (0.5 – 0.6)	< 0.001

6.4: Two Part Gamma Log Results for Healthcare Costs in the 24-Month Follow-up Period

Table 6.4.1: Covariate Coefficients from Two Part Model on Total Post Index Costs

	Two Part Model Log Coefficients			
Covariate	**Logit (SE)**	**p-value**	**Gamma (SE)**	**p-value**
Essential Tremor Diagnosis	0.677 (0.024)	<0.001	0.264 (0.017)	<0.001
Age (Years)	0.011 (0.001)	<0.001	-0.019 (0.001)	<0.001
Sex	0.034 (0.024)	0.170	0.009 (0.017)	0.594
Payer: Medicare (vs. Commercial)	0.599 (0.103)	<0.001	0.269 (0.030)	<0.001
Payer: Medicaid (vs. Commercial)	-3.070 (0.040)	<0.001	-0.080 (0.023)	<0.001
Index Year: 2016	-0.253 (0.052)	<0.001	-0.175 (0.031)	<0.001
Index Year: 2017	-0.449 (0.054)	<0.001	-0.189 (0.034)	<0.001
Index Year: 2018	-0.613 (0.054)	<0.001	-0.303 (0.037)	<0.001
Index Year: 2019	-0.668 (0.053)	<0.001	-0.295 (0.036)	<0.001
Index Year: 2020	-0.683 (0.054)	<0.001	-0.193 (0.039)	<0.001
Index Year: 2021	0.438 (0.066)	<0.001	-0.139 (0.037)	<0.001
Index Year: 2022	0.939 (0.097)	<0.001	-0.159 (0.039)	<0.001
Index Year: 2023	0.567 (0.232)	0.014	-0.221 (0.091)	0.016
Age-Adjusted CCI	0.063 (0.006)	<0.001	0.242 (0.005)	<0.001

** Coefficients and SE were produced by regression of the listed covariates on the total post index costs. Logit coefficients are from Part 1 of the Two-Part model; Gamma coefficients are from Part 2.*

Table 6.4.2: Covariate Coefficients from Two Part Model on Post Index Inpatient Costs

	Two Part Model Log Coefficients			
Covariate	**Logit (SE)**	**p-value**	**Gamma (SE)**	**p-value**
Essential Tremor Diagnosis	0.338 (0.014)	<0.001	-0.036 (0.042)	0.397
Age (Years)	-0.005 (0.001)	<0.001	-0.014 (0.002)	<0.001
Sex	0.035 (0.014)	0.015	-0.089 (0.042)	0.034
Payer: Medicare (vs. Commercial)	0.506 (0.024)	<0.001	-0.084 (0.073)	0.255
Payer: Medicaid (vs. Commercial)	0.502 (0.019)	<0.001	-0.453 (0.058)	<0.001
Index Year: 2016	-0.255 (0.024)	<0.001	-0.144 (0.070)	<0.001
Index Year: 2017	-0.421 (0.027)	<0.001	-0.050 (0.079)	0.528
Index Year: 2018	-0.471 (0.030)	<0.001	-0.277 (0.088)	0.002
Index Year: 2019	-0.593 (0.029)	<0.001	-0.206 (0.087)	0.018
Index Year: 2020	-0.678 (0.032)	<0.001	-0.062 (0.096)	0.517
Index Year: 2021	-0.564 (0.030)	<0.001	-0.090 (0.091)	0.324
Index Year: 2022	-0.625 (0.033)	<0.001	-0.413 (0.098)	<0.001
Index Year: 2023	-0.648 (0.081)	<0.001	-0.459 (0.242)	0.058
Age-Adjusted CCI	0.237 (0.004)	<0.001	0.080 (0.009)	<0.001

** Coefficients and SE were produced by regression of the listed covariates on the post index inpatient costs. Logit coefficients are from Part 1 of the Two-Part model; Gamma coefficients are from Part 2.*

Table 6.4.3: Covariate Coefficients from Two Part Model on Post Index Outpatient Costs

	Two Part Model Log Coefficients			
Covariate	**Logit (SE)**	**p-value**	**Gamma (SE)**	**p-value**
Essential Tremor Diagnosis	0.819 (0.023)	<0.001	0.193 (0.016)	<0.001
Age (Years)	0.006 (0.001)	<0.001	-0.016 (0.001)	<0.001
Sex	0.069 (0.023)	0.002	0.036 (0.016)	0.029
Payer: Medicare (vs. Commercial)	0.277 (0.070)	<0.001	0.264 (0.028)	<0.001
Payer: Medicaid (vs. Commercial)	-2.704 (0.033)	<0.001	0.014 (0.022)	0.510
Index Year: 2016	-0.204 (0.047)	<0.001	-0.081 (0.029)	0.005
Index Year: 2017	-0.397 (0.049)	<0.001	-0.086 (0.032)	0.007
Index Year: 2018	-0.518 (0.049)	<0.001	-0.164 (0.035)	<0.001
Index Year: 2019	-0.557 (0.048)	<0.001	-0.225 (0.034)	<0.001
Index Year: 2020	-0.635 (0.050)	<0.001	-0.099 (0.037)	0.007
Index Year: 2021	0.280 (0.058)	<0.001	0.028 (0.035)	0.425
Index Year: 2022	0.663 (0.078)	<0.001	0.014 (0.037)	0.709
Index Year: 2023	0.484 (0.196)	0.014	-0.066 (0.086)	0.443
Age-Adjusted CCI	0.085 (0.006)	<0.001	0.217 (0.005)	<0.001

** Coefficients and SE were produced by regression of the listed covariates on the post index outpatient costs. Logit coefficients are from Part 1 of the Two-Part model; Gamma coefficients are from Part 2.*

Table 6.4.4: Covariate Coefficients from Two Part Model on Post Index Emergency Department Costs

	Two Part Model Log Coefficients			
Covariate	**Logit (SE)**	**p-value**	**Gamma (SE)**	**p-value**
Essential Tremor Diagnosis	0.385 (0.011)	<0.001	0.128 (0.018)	<0.001
Age (Years)	-0.008 (0.001)	<0.001	-0.016 (0.001)	<0.001
Sex	0.161 (0.011)	<0.001	0.037 (0.018)	0.046
Payer: Medicare (vs. Commercial)	0.360 (0.019)	<0.001	0.012 (0.032)	0.704
Payer: Medicaid (vs. Commercial)	0.500 (0.014)	<0.001	-0.705 (0.024)	<0.001
Index Year: 2016	-0.216 (0.020)	<0.001	-0.013 (0.032)	0.694
Index Year: 2017	-0.318 (0.022)	<0.001	-0.005 (0.035)	0.878
Index Year: 2018	-0.376 (0.024)	<0.001	-0.178 (0.039)	<0.001
Index Year: 2019	-0.449 (0.024)	<0.001	-0.245 (0.038)	<0.001
Index Year: 2020	-0.480 (0.025)	<0.001	-0.275 (0.041)	<0.001
Index Year: 2021	-0.217 (0.024)	<0.001	-0.209 (0.039)	<0.001
Index Year: 2022	-0.175 (0.026)	<0.001	-0.244 (0.041)	<0.001
Index Year: 2023	-0.187 (0.061)	0.002	-0.305 (0.097)	0.002
Age-Adjusted CCI	0.202 (0.003)	<0.001	0.115 (0.005)	<0.001

** Coefficients and SE were produced by regression of the listed covariates on the post index emergency department costs. Logit coefficients are from Part 1 of the Two-Part model; Gamma coefficients are from Part 2.*

Table 6.4.5: Covariate Coefficients from Two Part Model on Post Index Pharmacy Costs

	Two Part Model Log Coefficients			
Covariate	**Logit (SE)**	**p-value**	**Gamma (SE)**	**p-value**
Essential Tremor Diagnosis	0.426 (0.015)	<0.001	0.328 (0.033)	<0.001
Age (Years)	-0.019 (0.001)	<0.001	-0.031 (0.002)	<0.001
Sex	0.078 (0.016)	<0.001	0.018 (0.033)	0.574
Payer: Medicare (vs. Commercial)	0.979 (0.034)	<0.001	0.208 (0.056)	<0.001
Payer: Medicaid (vs. Commercial)	-2.588 (0.019)	<0.001	-0.169 (0.047)	<0.001
Index Year: 2016	-0.014 (0.029)	0.631	-0.141 (0.058)	0.015
Index Year: 2017	-0.073 (0.031)	0.019	-0.214 (0.064)	<0.001
Index Year: 2018	-0.186 (0.032)	<0.001	-0.226 (0.072)	0.002
Index Year: 2019	-0.060 (0.032)	0.061	-0.085 (0.069)	0.215
Index Year: 2020	0.013 (0.034)	0.701	-0.019 (0.074)	0.803
Index Year: 2021	0.395 (0.035)	<0.001	-0.011 (0.070)	0.879
Index Year: 2022	0.415 (0.041)	<0.001	0.069 (0.072)	0.335
Index Year: 2023	0.002 (0.096)	0.984	0.052 (0.170)	0.760
Age-Adjusted CCI	0.072 (0.004)	<0.001	0.260 (0.010)	<0.001

** Coefficients and SE were produced by regression of the listed covariates on the post index pharmacy prescription costs. Logit coefficients are from Part 1 of the Two-Part model; Gamma coefficients are from Part 2.*

Table 6.4.6: Average Treatment Effect on the Treated (ATT) of Healthcare Costs in the 24-Month Follow-up Period

Cost Category	ATT [95% CI]
Total costs	9,927.92 (8797.56, 11,019.98)
Inpatient costs	1,869.44 (1,204.81, 2,463.65)
Outpatient costs	3,706.73 (3,238.70, 4,208.86)
ED costs	609.21 (540.11, 677.49)
Pharmacy costs	2,771.02 (2,366.20, 3,248.70)

Table 6.4.7: Number of Patients with Zero Healthcare Costs in the 24-Month Follow-up Period

Cost Category	Overall (%)	ET (%)	General Population (%)
Total costs	8,817 (6.49)	3,290 (4.55)	5,527 (7.64)
Inpatient costs	116,440 (80.48)	56,608 (78.25)	59,832 (82.71)
Outpatient costs	10,420 (7.20)	3,594 (4.97)	6,826 (9.44)
ED costs	84,552 (58.44)	39,216 (54.21)	45,336 (62.67)
Pharmacy costs	33,193 (22.94)	14,720 (20.35)	18,473 (25.54)

6.5: Negative Binomial Model Results for Healthcare Resource Utilization in the 24-Month Follow-up Period

Table 6.5.1: Covariate Coefficients from Negative Binomial Regression on Total Post Index Encounters

Covariate	Log Coefficient (SE)	p-value
Essential Tremor Diagnosis	0.275 (0.005)	< 0.001
Age (Years)	-0.006 (0.0003)	< 0.001
Sex	0.164 (0.006)	< 0.001
Payer: Medicare (vs. Commercial)	0.141 (0.009)	< 0.001
Payer: Medicaid (vs. Commercial)	1.101 (0.007)	< 0.001
Index Year: 2016	-0.084 (0.010)	< 0.001
Index Year: 2017	-0.068 (0.011)	< 0.001
Index Year: 2018	-0.044 (0.012)	< 0.001
Index Year: 2019	-0.081 (0.012)	< 0.001
Index Year: 2020	-0.050 (0.012)	< 0.001
Index Year: 2021	-0.024 (0.012)	< 0.05
Index Year: 2022	0.002 (0.013)	0.848
Index Year: 2023	-0.019 (0.030)	0.520
Age-Adjusted CCI	0.152 (0.002)	< 0.001

** Coefficients and SE were produced by a negative binomial regression of the listed covariates on the overall total number of post index encounters.*

Table 6.5.2: Covariate Coefficients from Negative Binomial Regression from Post Index Inpatient Encounters

Covariate	Log Coefficient (SE)	p-value
Essential Tremor Diagnosis	0.348 (0.012)	< 0.001
Age (Years)	-0.017 (0.0006)	< 0.001
Sex	-0.0007 (0.013)	0.955
Payer: Medicare (vs. Commercial)	0.594 (0.021)	< 0.001
Payer: Medicaid (vs. Commercial)	0.909 (0.016)	< 0.001
Index Year: 2016	-0.260 (0.022)	< 0.001
Index Year: 2017	-0.375 (0.024)	< 0.001
Index Year: 2018	-0.354 (0.026)	< 0.001
Index Year: 2019	-0.455 (0.026)	< 0.001
Index Year: 2020	-0.493 (0.028)	< 0.001
Index Year: 2021	-0.547 (0.027)	< 0.001
Index Year: 2022	-0.548 (0.029)	< 0.001
Index Year: 2023	-0.537 (0.071)	< 0.001
Age-Adjusted CCI	0.241 (0.003)	< 0.001

** Coefficients and SE were produced by a negative binomial regression of the listed covariates on the total number of post index inpatient encounters.*

Table 6.5.3: Covariate Coefficients from Negative Binomial Regression from Post Index Outpatient Encounters

Covariate	Log Coefficient (SE)	p-value
Essential Tremor Diagnosis	0.271 (0.016)	< 0.001
Age (Years)	-0.005 (0.0003)	< 0.001
Sex	0.165 (0.006)	0.955
Payer: Medicare (vs. Commercial)	0.123 (0.010)	< 0.001
Payer: Medicaid (vs. Commercial)	1.097 (0.007)	< 0.001
Index Year: 2016	-0.077 (0.010)	< 0.001
Index Year: 2017	-0.058 (0.011)	< 0.001
Index Year: 2018	-0.033 (0.012)	0.007
Index Year: 2019	-0.069 (0.012)	< 0.001
Index Year: 2020	-0.038 (0.013)	0.003
Index Year: 2021	-0.011 (0.012)	0.382
Index Year: 2022	0.015 (0.013)	0.256
Index Year: 2023	-0.008 (0.031)	0.793
Age-Adjusted CCI	0.149 (0.002)	< 0.001

** Coefficients and SE were produced by a negative binomial regression of the listed covariates on the total number of post index outpatient encounters.*

Table 6.5.4: Covariate Coefficients from Negative Binomial Regression from Post Index Emergency Department Encounters

Covariate	Log Coefficient (SE)	p-value
Essential Tremor Diagnosis	0.384 (0.009)	< 0.001
Age (Years)	-0.026 (0.0004)	< 0.001
Sex	0.133 (0.009)	< 0.001
Payer: Medicare (vs. Commercial)	0.760 (0.015)	< 0.001
Payer: Medicaid (vs. Commercial)	1.313 (0.011)	< 0.001
Index Year: 2016	-0.249 (0.016)	< 0.001
Index Year: 2017	-0.333 (0.017)	< 0.001
Index Year: 2018	-0.342 (0.019)	< 0.001
Index Year: 2019	-0.414 (0.019)	< 0.001
Index Year: 2020	-0.392 (0.020)	< 0.001
Index Year: 2021	-0.376 (0.019)	< 0.001
Index Year: 2022	-0.310 (0.021)	< 0.001
Index Year: 2023	-0.282 (0.049)	< 0.001
Age-Adjusted CCI	0.210 (0.002)	< 0.001

** Coefficients and SE were produced by a negative binomial regression of the listed covariates on the total number of post index emergency department visits.*

Table 6.6: Negative Binomial Model Results for Healthcare Resource Utilization in the 24-Month Follow-up Period

Encounter Category	Log Coefficient (SE)	Incident Rate Ratio (IRR) [95% CI]	p-value
Total encounters	0.28 (0.01)	1.32 [1.30, 1.33]	< 0.001
Inpatient admissions	0.35 (0.01)	1.42 [1.38, 1.45]	< 0.001
Outpatient visits	0.27 (0.01)	1.31 [1.30, 1.33]	< 0.001
ED visits	0.38 (0.01)	1.47 [1.44, 1.49]	< 0.001

Table 6.7: Negative Binomial Regression Results: Average Marginal Effects of Essential Tremor on Healthcare Resource Utilization in the 24-Month Follow-up Period

Encounter Category	AME [95% CI]
Total encounters	17.660 (16.960, 18.370)
Inpatient admissions	0.135 (0.125, 0.144)
Outpatient visits	16.830 (16.130, 17.520)
ED visits	0.670 (0.639, 0.701)

6.8: Sensitivity Analysis of Regression Models on the Average Treatment Effect on the Treated (ATT) in the 24-Month Follow-up Period

Table 6.8.1: Regression Model Sensitivity Analysis on the Average Treatment Effect on the Treated (ATT) in the 24-Month Follow-up Period

	Regression Model – Mean ATT*				
	OLS	**Two-Part Logit logNormal**	**Gamma Link Identity**	**Winsorized (0.99) OLS**	**Winsorized (0.99) Two-Part Gamma Log link**
Total Costs	5,995.32	6,519.81	(Fails)	6,820.09	9,385.40
Outpatient Costs	1,718.67	2,630.48		2,870.14	3,845.33
**Mean ATT for all models were constructed via the method of recycled predictions.*					

Table 6.8.2: Sensitivity Analysis using Tweedie Family Regression Model on the Average Treatment Effect on the Treated (ATT) in the 24-Month Follow-up Period

	Variance Power Parameter					
	1.0	**1.1**	**1.2**	**1.5**	**1.7**	**1.9**
Total Costs	6,546	6,846	7,455	8,079	8,718	9,373
Outpatient Costs	1,973	2,131	2,443	2,751	3,058	3,366

Figure 1. Study Timeline Diagram

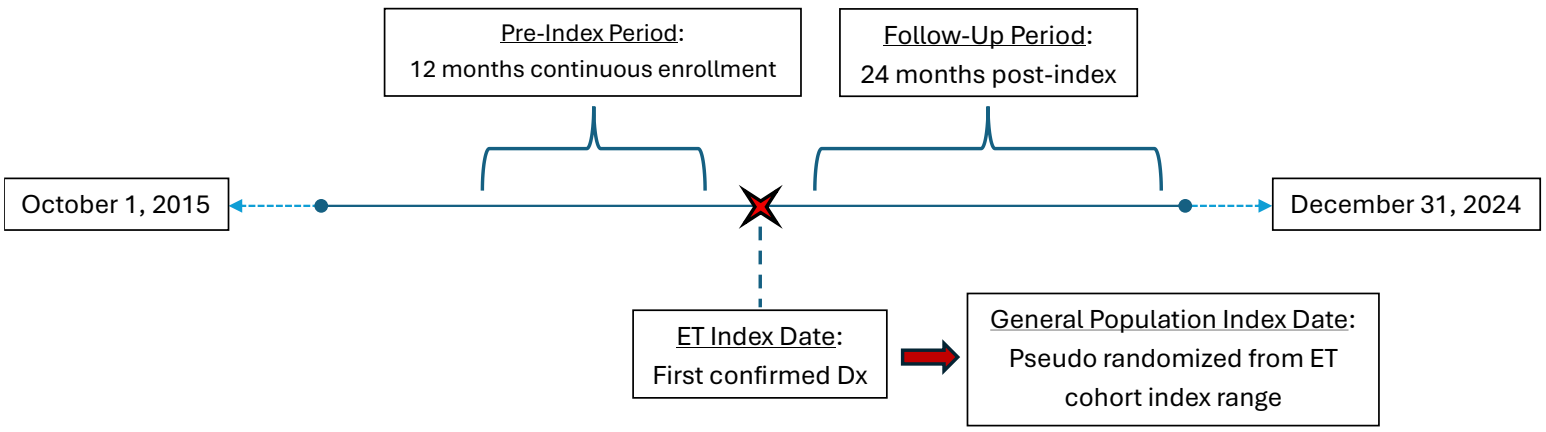


Figure 2.1 Essential Tremor Cohort Attrition Diagram

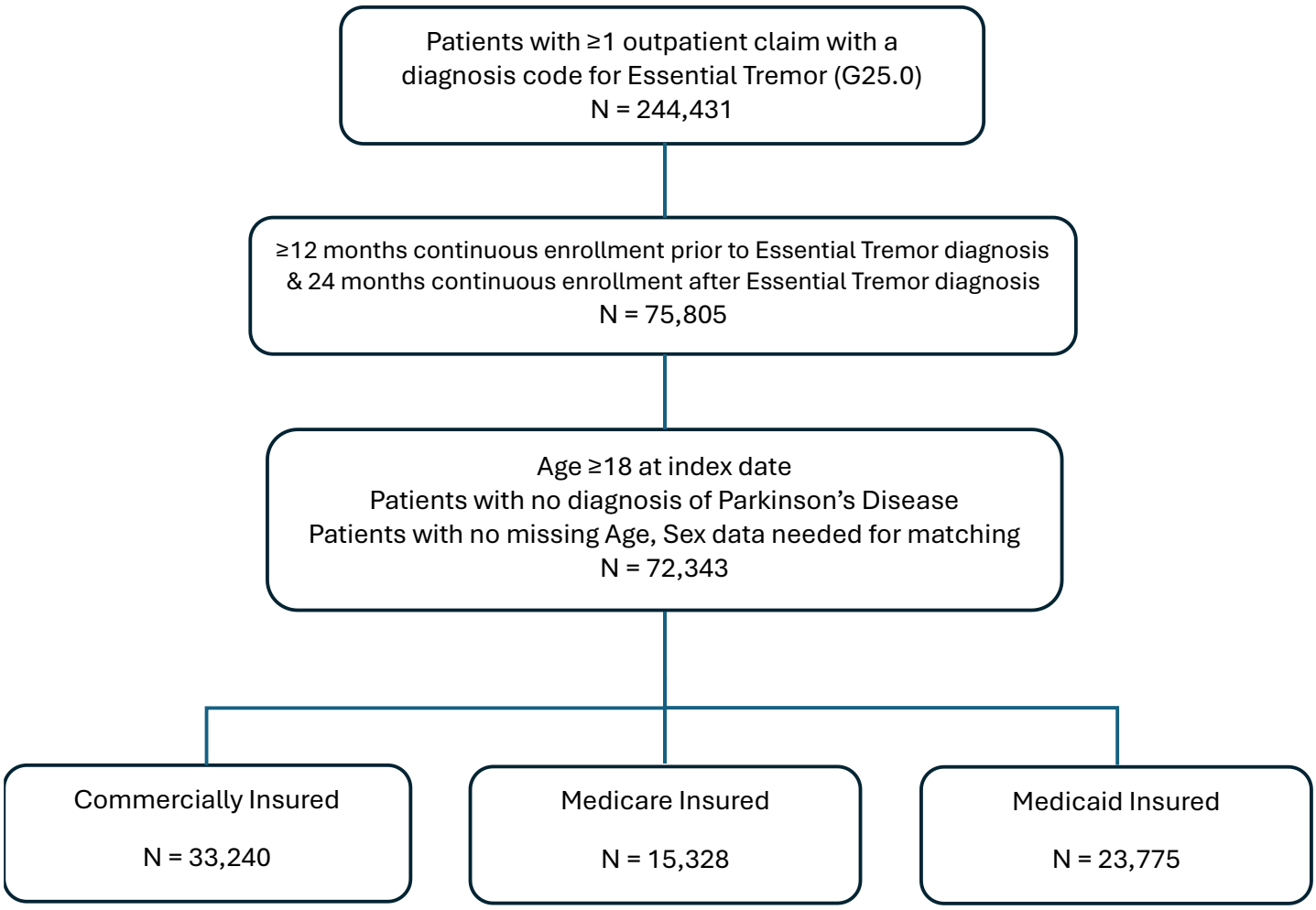


Figure 2.2 General Population Cohort Attrition Diagram

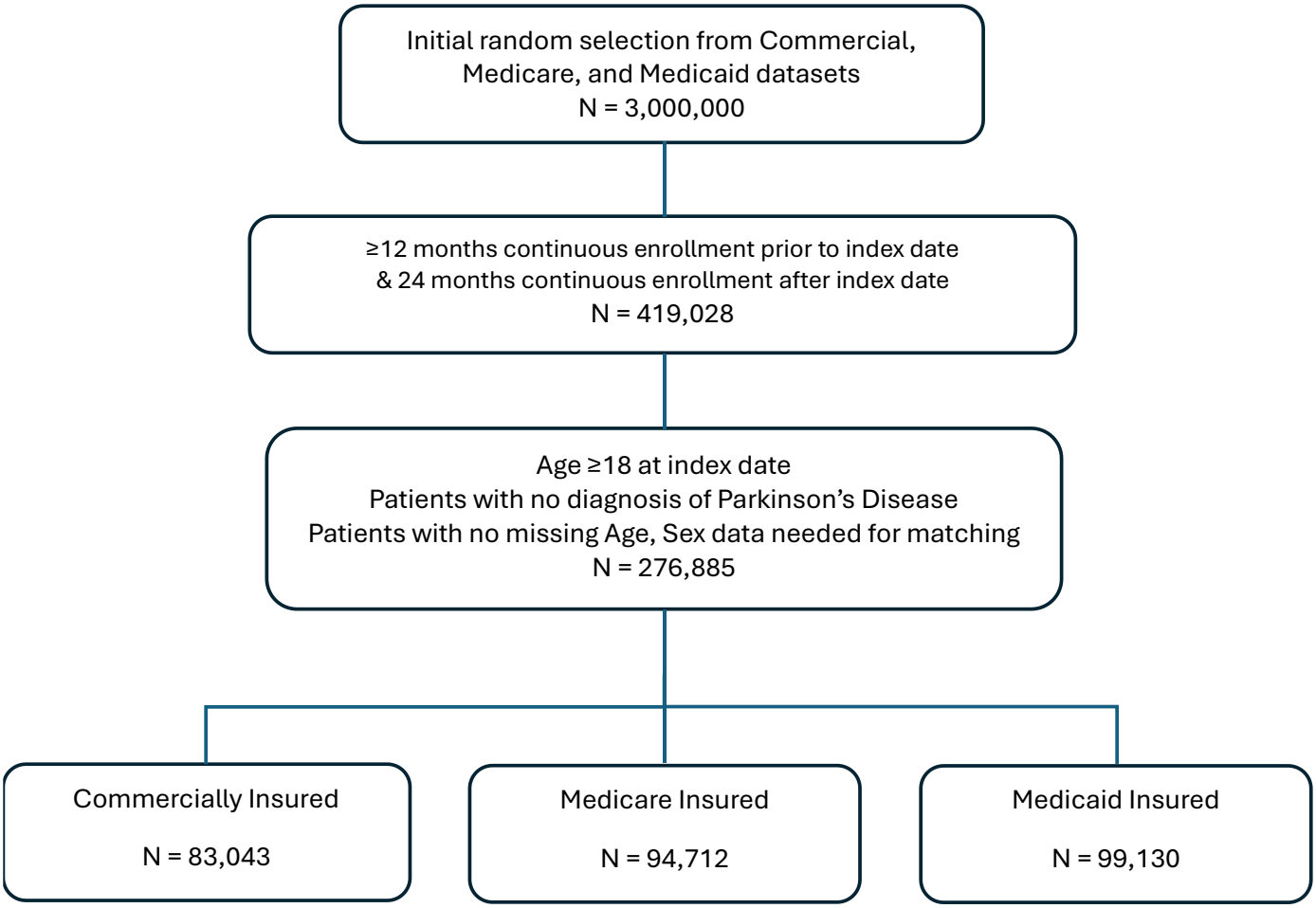
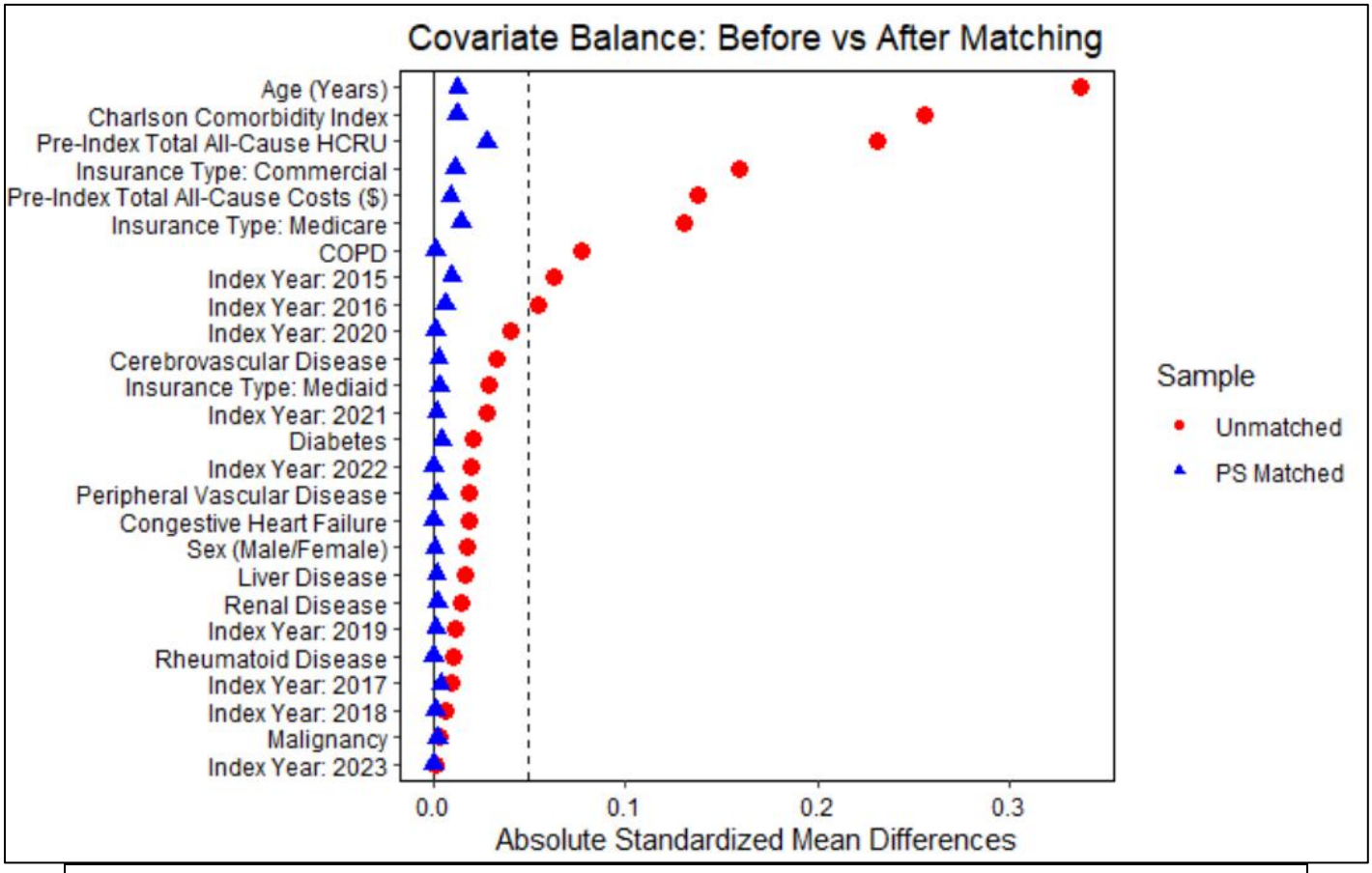


Figure 3. Love Plot: Covariate Balance between the Essential Tremor and Matched General Population Cohorts



**COPD: Chronic Obstructive Pulmonary Disease; HCRU: Healthcare Resource Utilization*

Figure 4. Mean Post-Index Costs by Category for the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

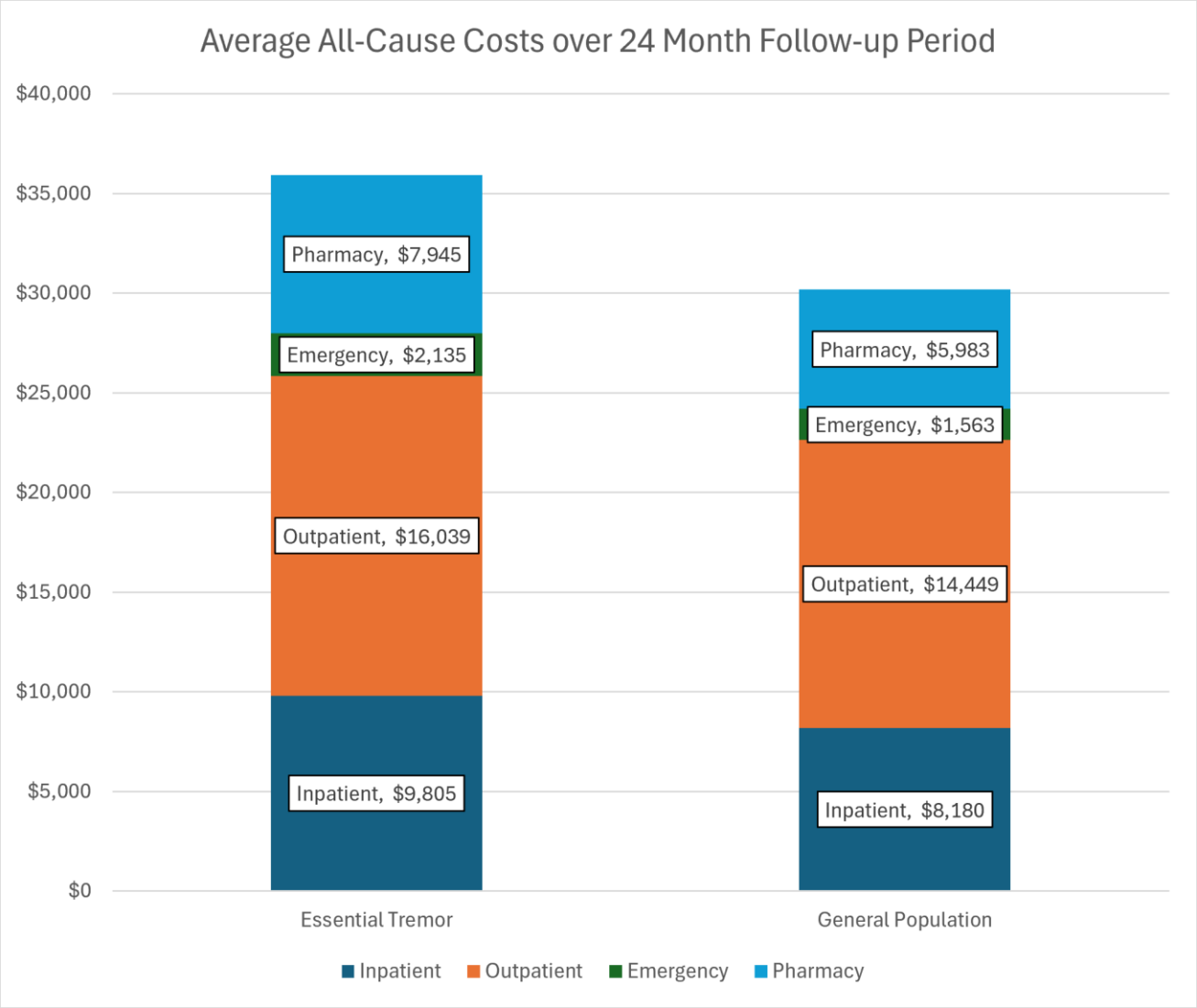
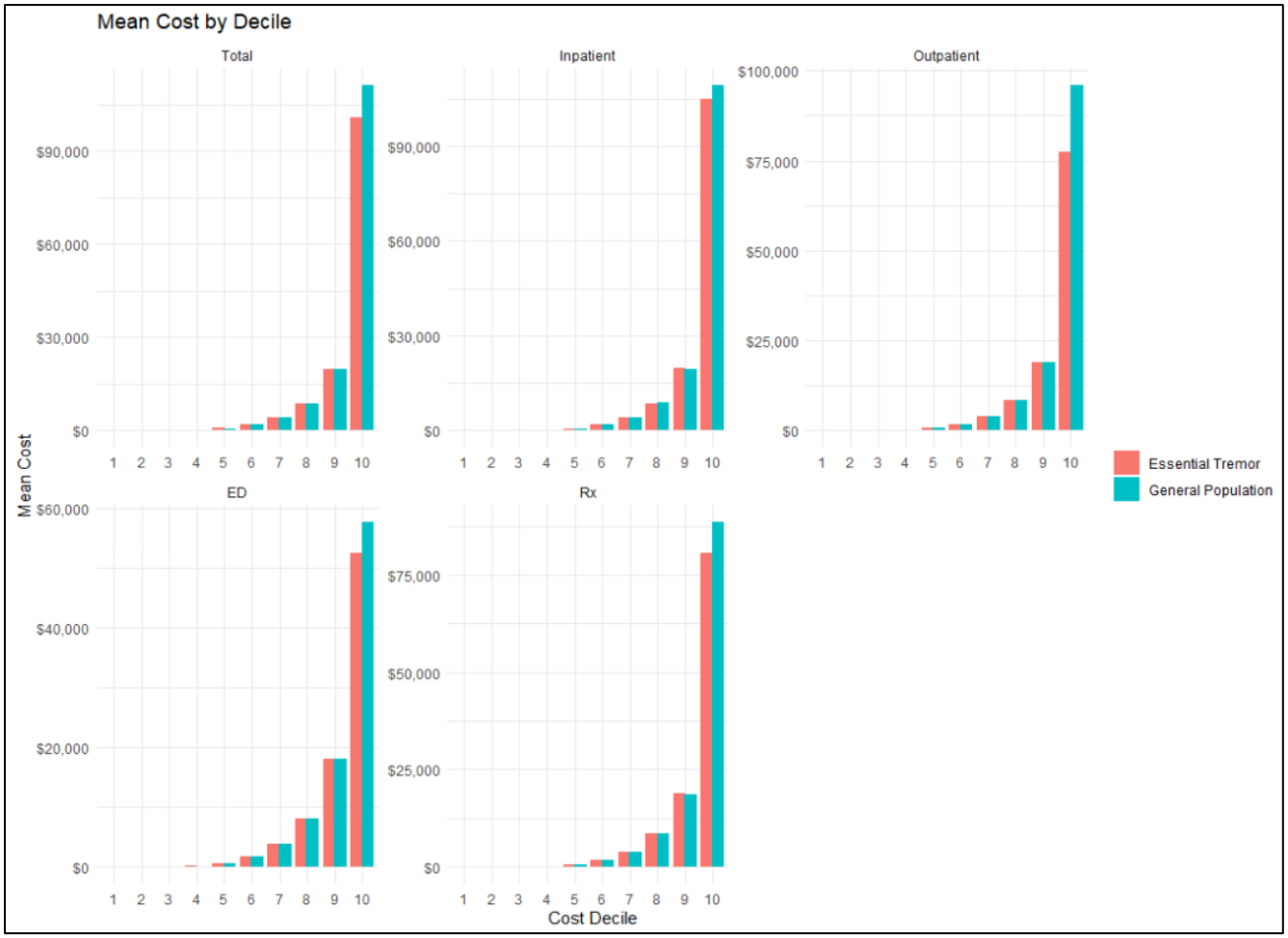


Figure 5. Mean Post-Index Costs by Decile and Category for the Matched ET and General Population Cohorts in the 24-Month Follow-up Period



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8. Appendices

Appendix A. Baseline Characteristics* of ET Patients and General Population Controls – Before Matching

	ET n = 72,343	General Population n = 276,885
Age		
Mean (SD†)	58.7 (16.0)	53.3 (19.1)
Median (IQR†)	59.0 (50.0, 70.0)	55.0 (37.0, 69.0)
Range (Min – Max)	18.0 – 105.0	18.0 – 103.0
Sex, %		
Male	43.9%	42.1%
Female	56.1%	57.9%
Insurance Plan type, %		
Commercial	45.9%	30.0%
Medicare	21.2%	34.2%
Medicaid	32.9%	35.8%
Index Year, %		
2015	11.8%	5.5%
2016	22.7%	17.3%
2017	14.9%	15.8%
2018	10.7%	11.4%
2019	11.8%	12.9%
2020	9.2%	13.2%
2021	9.9%	12.7%
2022	8.1%	10.1%
2023	0.9%	1.1%
Charlson Comorbidity Index (CCI)		
Mean (SD†)	2.8 (2.5)	2.2 (2.4)
Median (IQR†)	2.0 (1.0, 4.0)	2.0 (0.0, 4.0)
Range (Min – Max)	0.0 – 21.0	0.0 – 21.0
Comorbidities, %		
COPD†	20.8%	13.1%
Congestive Heart Failure	6.3%	4.5%
Diabetes	11.8%	9.7%
Peripheral Vascular Disease	8.0%	6.1%
Cerebrovascular Disease	8.3%	5.0%

Renal Disease	6.7%	5.3%
Liver Disease	4.8%	3.1%
Malignancy	5.6%	5.3%
Rheumatoid Disease	3.1%	2.0%
Total All-Cause Pre-Index Costs ($)		
Mean (SD†)	15,421.69 (41,963.80)	9,652.23 (34,924.12)
Median (IQR†)	4,618.57 (1,168.88, 14,521.24)	1,845.20 (282.17, 7,319.01)
Range (Min – Max)	0.00 – 2,639,997.30	0 – 3,450,928.15
Total All-Cause Pre-Index Encounters, n		
Mean (SD†)	31.6 (54.7)	18.9 (40.8)
Median (IQR†)	16.0 (7.0, 32.0)	9.0 (3.0, 19.0)
Range (Min – Max)	0.0– 414.0	0.0 – 422.0
** Baseline characteristics: Covariates used in matching that were collected during 12-month pre-index period.* *† SD: Standard Deviation; IQR: Interquartile Range; SMD: Standardized Mean Difference; COPD: Chronic Obstructive Pulmonary Disease*		

Appendix B. ICD-10 Diagnosis Codes

ICD-10 Code	Description
G25.0	Essential Tremor
G21.0	Parkinson's Disease
F41.1, F41.3, F41.9	Anxiety
F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F32.A, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.9	Depression
F10.x	Alcohol Substance Abuse
I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	Chronic Obstructive Pulmonary Disorder
I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0	Congestive Heart Failure
E10.0, E10.1, E10.6, E10.8, E10.9,E11.0, E11.1, E11.6, E11.8, E11.9,E12.0, E12.1, E12.6, E12.8, E12.9,E13.0, E13.1, E13.6, E13.8, E13.9,E14.0, E14.1, E14.6, E14.8, E14.9	Diabetes
I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	Peripheral Vascular Disease
G45.x, G46.x, H34.0, I60.x–I69.x	Cerebrovascular Disease
I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	Renal Disease
B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4	Liver Disease
C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x	Malignancy
M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0	Rheumatoid Disease

Appendix C. Place of Service Codes and Descriptions

Code	Place of Service
STDPLAC - Inpatient Codes	
21	Inpatient Hospital
51	Inpatient Psychiatric Facility
55	Residential Substance Abuse Facility
56	Psych Residential Treatment Center
61	Comprehensive Inpatient Rehab Facility
STDPLAC – Outpatient Codes	
2	Telehealth
10	Telehealth Provided in Patient Home
11	Office
12	Patient Home
17	Walk-in Retail Health Clinic
19	Outpatient Hospital – Off Campus
20	Urgent Care Facility
22	Outpatient Hospital – On Campus
25	Birthing Center
49	Independent Clinic
50	Federally Qualified Health Center
52	Psych Facility Partial Hospital
53	Community Mental Health Center
57	Non-Resident Substance Abuse Facility
60	Mass Immunization Center
62	Comprehensive Outpatient Rehab Facility
65	End-Stage Renal Disease Facility
71	State/Local Public Health Clinic
72	Rural Health Clinic
95	Outpatient (Not Elsewhere Classified)
STDPLAC – Emergency Room	
23	Emergency Room – Hospital
REVCODE	
0450	Emergency Room - General
0451	Emergency Medical Screening Services
0452	ER – Screening
0456	Urgent Care

0459	Emergency Room - Other
0981	Professional Fee – Emergency Room
PROC1 Codes	
99281	Emergency Department Evaluation and Management – Level 1
99282	Emergency Department Evaluation and Management – Level 2
99283	Emergency Department Evaluation and Management – Level 3
99284	Emergency Department Evaluation and Management – Level 4
99285	Emergency Department Evaluation and Management – Level 5
SVCSCAT	
10120	Facility Inpatient Non-Acute ER
10220	Facility Inpatient Longterm Care ER
10320	Facility Inpatient Maternity ER
10420	Facility Inpatient Surgical ER
10520	Facility Inpatient Medical ER
12220	Facility Outpatient ER
20120	Physician Specialty Inpatient ER
20220	Physician Non-Specialty Inpatient ER
21120	Physician Specialty Outpatient ER
21220	Physician Non-Specialty Outpatient ER
22120	Professional Inpatient ER
22320	Professional Outpatient ER
30120	Mental Health Facility Inpatient ER
30220	Mental Health Physician Inpatient ER
30320	Mental Health Professional Inpatient ER
30420	Mental Health Facility Outpatient ER
30520	Mental Health Physician Outpatient ER
30620	Mental Health Professional Outpatient ER
31120	Substance Abuse Facility Inpatient ER
31220	Substance Abuse Physician Inpatient ER
31320	Substance Abuse Professional Inpatient ER
31420	Substance Abuse Facility Outpatient ER
31520	Substance Abuse Physician Outpatient ER
31620	Substance Abuse Professional Outpatient ER

Appendix D. Healthcare Resource Utilization Service Location Schema

	Variable Names and Codes			
	STDPLAC	REVCODE	PROC1	SVCSCAT
Inpatient	21, 51, 55, 56, 61			
Outpatient	2, 10, 11, 12, 17, 19, 20, 22, 25, 49, 50, 52, 53, 57, 60, 62, 65, 71, 72, 95			
Emergency Department	23	0450, 0451, 0452, 0456, 0459, 0981	99281, 99282, 99283, 99284, 99285	Entries ending in 20

Appendix E. Distribution of All-cause Healthcare Cost Data for the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

Figure E.1: Proportion of Individuals with Zero Costs in the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

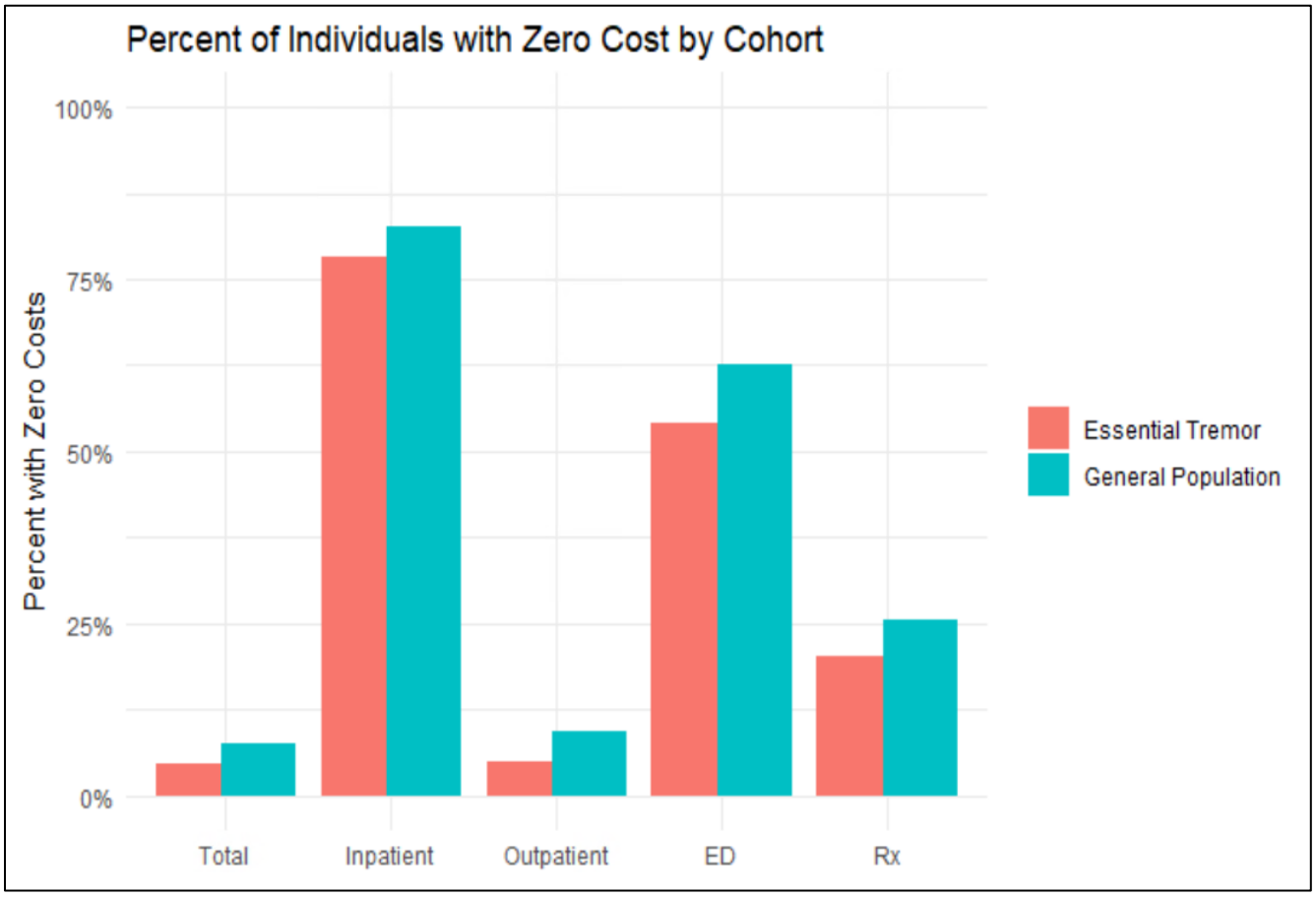


Figure E.2: Distribution of Individuals with Positive Costs (> $0) in the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

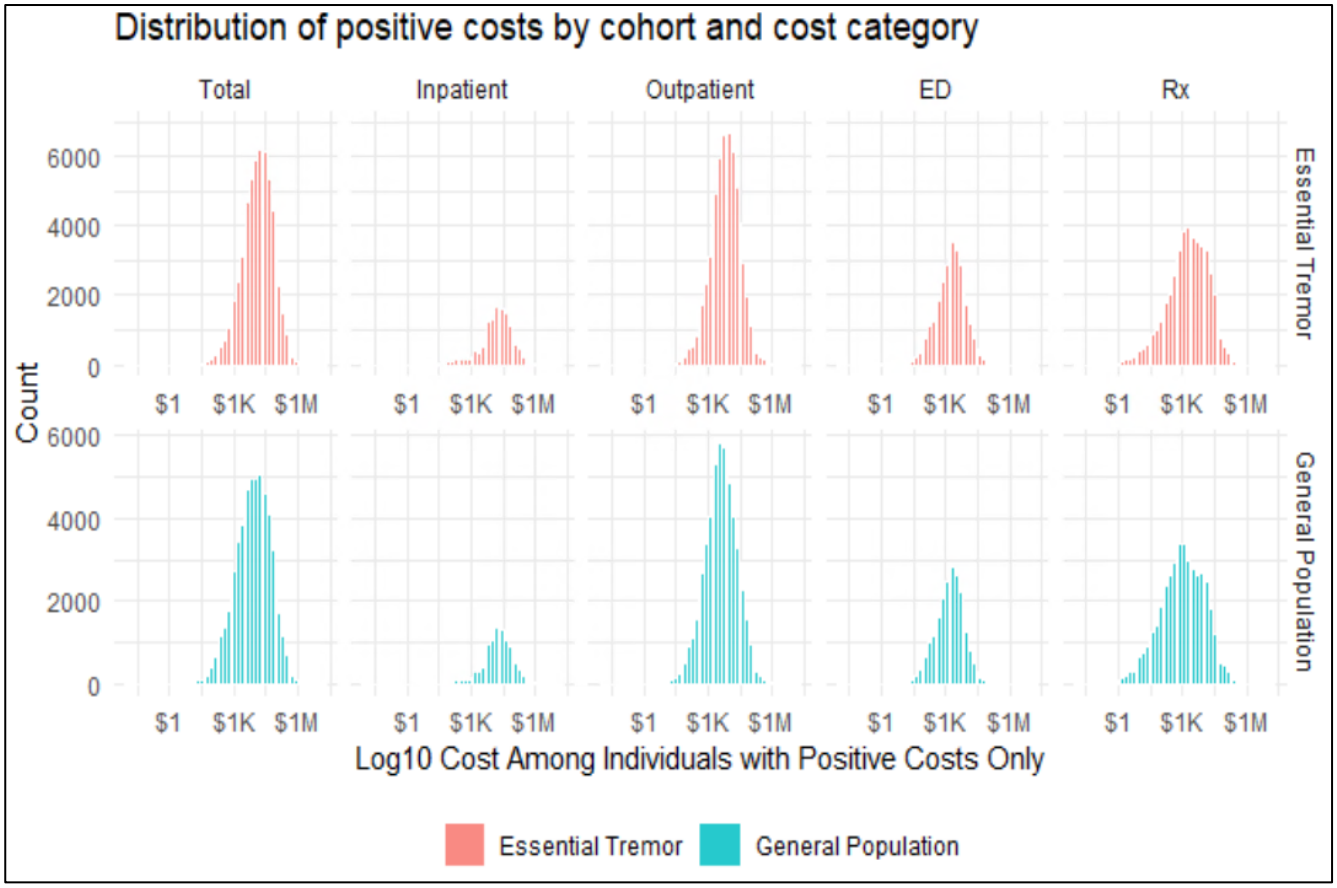


Figure E.3: Cumulative Proportion of Individuals with Positive Costs (> $0) in the Matched ET and General Population Cohorts in the 24-Month Follow-up Period

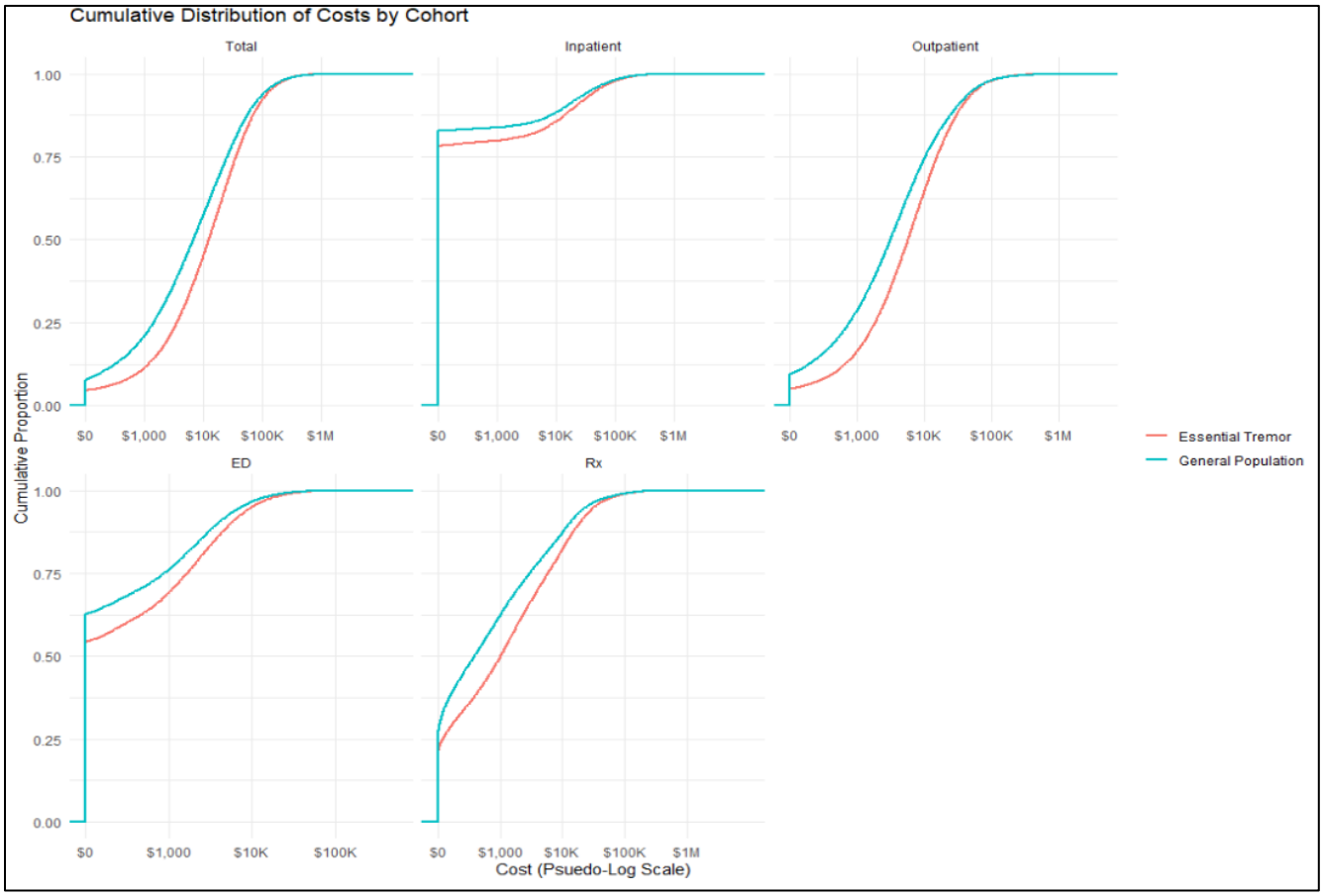
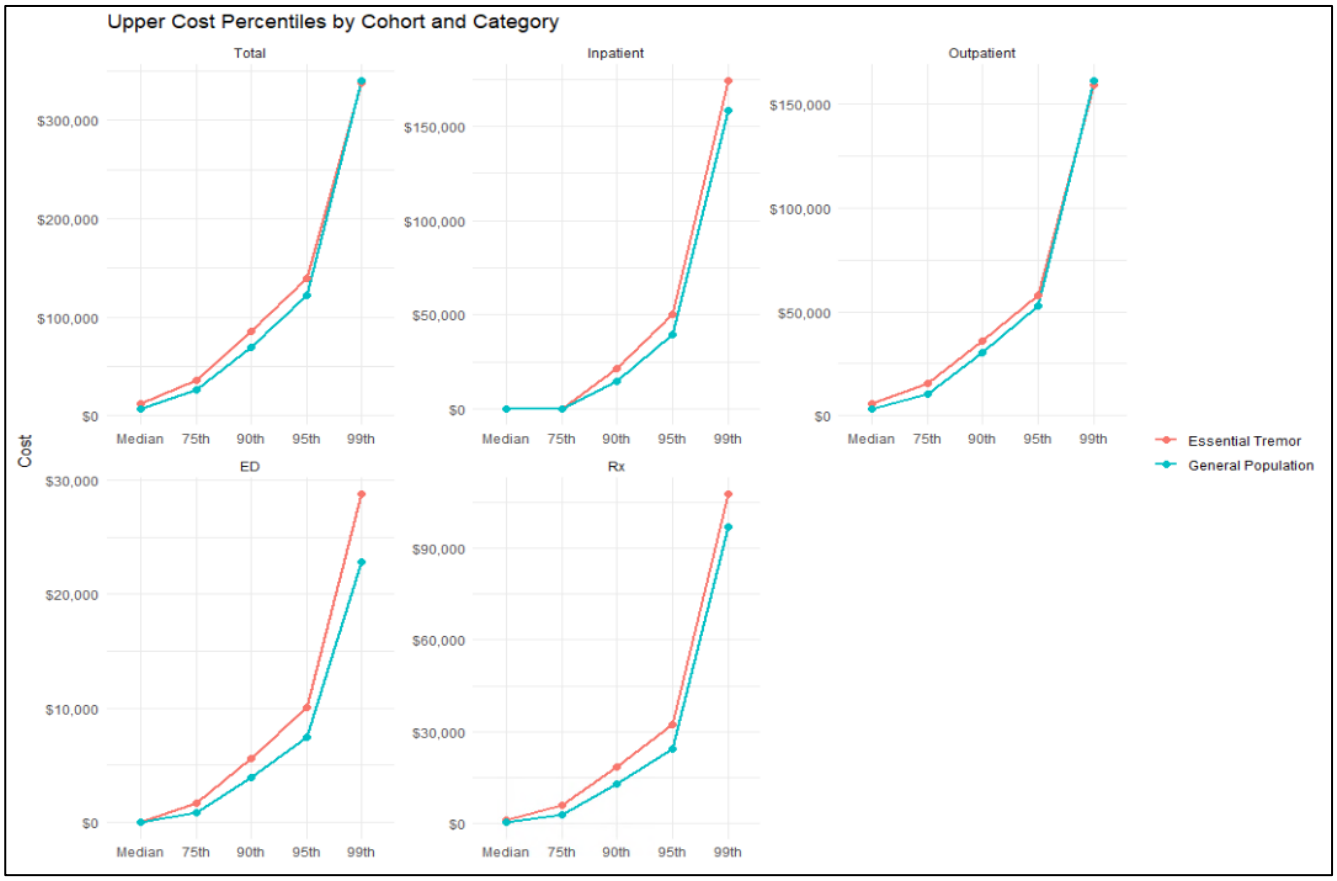


Figure E.3: Upper Percentile Distribution of Individuals with Positive Costs (> $0) in the Matched ET and General Population Cohorts in the 24-Month Follow-up Period



Appendix F. Residuals from Two-Part Model on Healthcare Costs in the 24-Month Follow-up Period

Figure F.1: Residuals from Part 1 Logit of the Two-Part Model on Healthcare Costs in the 24-Month Follow-up Period

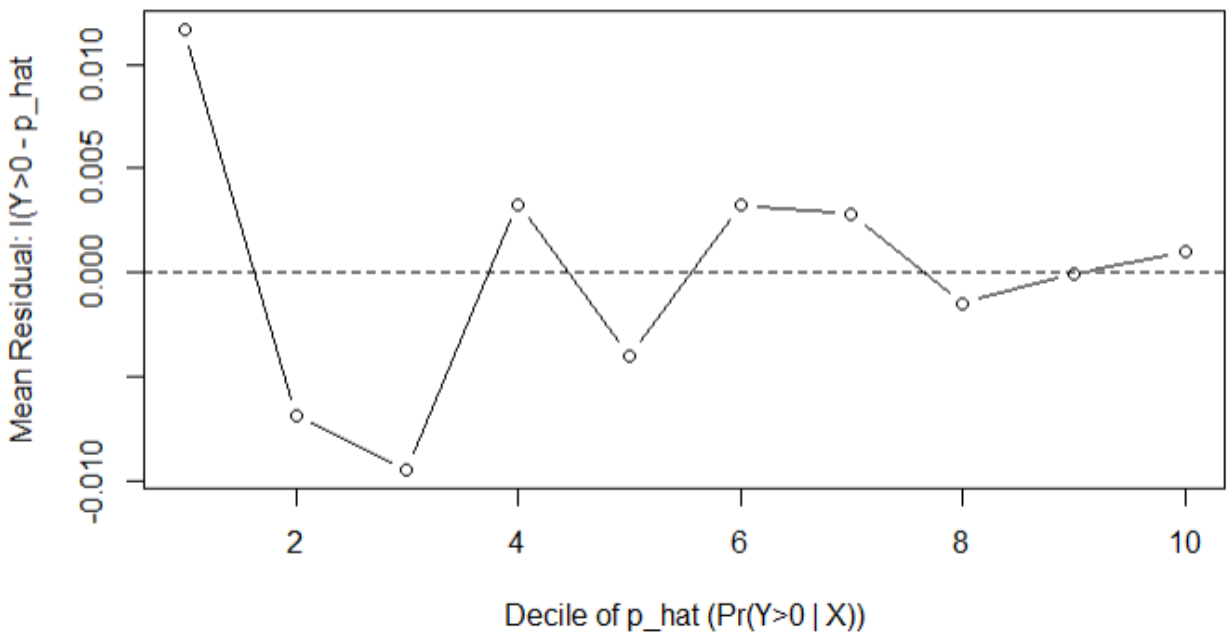


Figure F.2: Residuals from Part 2 Gamma Log Link of the Two-Part Model on Healthcare Costs in the 24-Month Follow-up Period

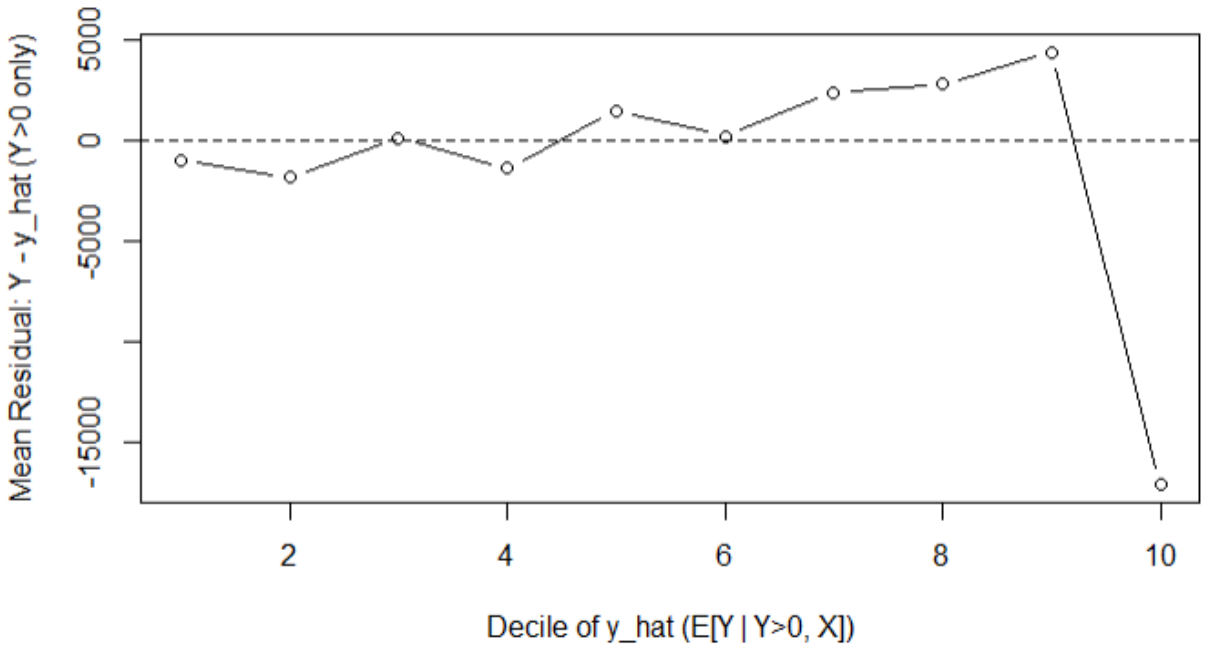


Figure F.3: Residuals from the Combined Parts of the Two-Part Model on Healthcare Costs in the 24-Month Follow-up Period