Early Steps Towards a Huntington's Disease Burden-of-Illness Model: Estimating Out-of-Pocket Costs for Patients Showing Clinical Symptoms

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Introduction and Background

Huntington's Disease (HD) is a rare, neurodegenerative disease caused by an expansion of the CAG repeat structure in the Huntington gene. Over time, the resultant mutant Huntington protein (mHTT) leads to debilitating motor, cognitive, and behavioural symptoms. An outstanding problem in the health economics of HD is to accurately quantify the disease's burden, both for the person with HD (PwHD) and their wider social network.

HD Charge (CinicalTrials.gov identifier: NCT03628235) is a multi-site, cross-sectional study aimed at addressing this question. In particular, it seeks to quantify indirect and out-of-pocket costs associated with HD. 233 individuals were surveyed across the United States and asked to report spending across 15 categories. Of the 233 participants, 124 were PwHD's (CAG length $\geq$ 40, UHDRS diagnostic confidence level of 4 [5]), 109 were companions of PwHD's, and 170 belonged to a PwHD/companion dyad. (Belonging to a dyad means that the PwHD and companion are in a relationship or partnership. In most cases, both participated in the survey.) Participants were classified into early, middle, and late stages according to Shoulson and Fahn's Total Functioning Capacity (TFC) for HD severity classification [3]. After pre-processing the raw survey data, we estimated annual HD-related out-of-pocket spending as a function of participant type (PwHD or companion), stage (early, middle, or late), and expenditure category (see table 1 for further information). Our methods and results represent early steps towards a comprehensive burden-of-illness model that seeks to estimate the economic burden of HD as it progresses over time.

Category	Recall Time	Notes
Medical Care	1 month	
Home Healthcare	1 month	
Non-health Assistive Care	1 month	
Help Outside the Home (1)	1 month	For PwHD
Home Maintenance	1 month	
Travel/Transportation (1)	1 month	For PwHD
Property Damage (low)	1 month	Low-cost items
Property Damage (high)	3 months	High-cost items
Medications	3 months	
Custodial Care	3 months	
Medical Equipment	6 months	
Food Delivery	1 month	
Help Outside the Home (2)	1 month	For companion
Travel Transport (2)	1 month	For companion/others
Other	6 months	Write-in responses

Table 1: Expenditure categories included in the analysis. The second column refers to the time frame prior to survey completion over which participants were asked to report spending.

N = 233	**Early**	**Middle**	**Late**
PwHD	38	56	30
Companion	27	44	38

Table 2: Sample sizes based on participant type and the associated PwHD's stage. Not all participants in the survey belong to a dyad. Stages are defined as follows: $11 \leq$ TFC $\leq 13 \iff$ early, $7 \leq$ TFC $\leq 10 \iff$ middle, $0 \leq$ TFC $\leq 6 \iff$ late. All PwHD's had a motor diagnosis and fall within stages 2 or 3 on the Huntingon's Disease Integrated Staging System [4].

Methods

All our estimates derive from fitting a generalized linear mixed model (GLMM) with the following mean structure:

$$\log\left(\mathrm{E}\left[Y_{dtc}\right]\right) = \alpha + \beta_d + \beta_t + \beta_c + \log \tau_c, \qquad (1)$$

where

- Subscripts d, t, c refer to a specific dyad, participant type, and category respectively. The complete triple (d, t, c) corresponds to a single survey response.
- $Y_{(\cdot)}$ is the reported cost for some combination of the above covariates.
- α, β_t, and β_c are population-level effects.
- $\beta_d \sim \mathcal{N}(0, \sigma)$ is a dyad-specific random effect. This can be thought of as controlling for unexplained spending patterns within a particular family unit.
- The final term offsets the varying timescales to which different expenditure categories apply.

We chose for $Y_{(\cdot)}$ to be Tweedie-distributed [2] due to the ease with which the Tweedie handles both outliers and zero inflation. The caption of figure 1 gives further details. Inference was performed via parametric bootstrapping. Under this approach, the fitted model – as determined by maximum likelihood – is used to simulate a large number of hypothetical data sets. The model is re-fit to each of these and the resulting parameter estimates are combined to form confidence intervals.

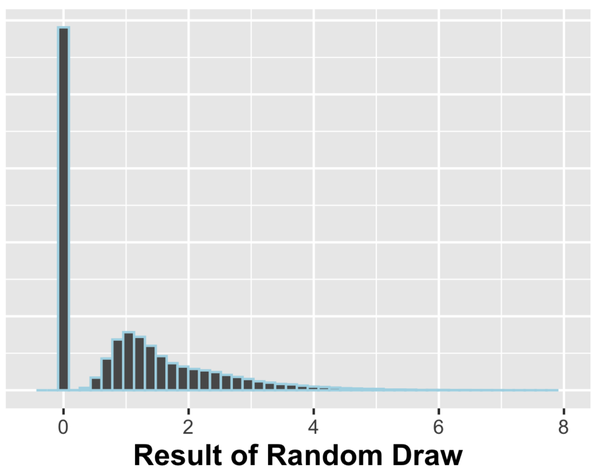

Figure 1: Simulating from a Tweedie distribution with mean $\mu = 1$, dispersion $\phi = 1.3$, and power parameter $\xi = 1.1$. The Tweedie has a variance structure given by $V(\mu) = \phi\mu^{\xi}$. When $\xi \in (1, 2)$, this distribution is equivalent to a sum of Gamma random variables where the number of terms in the sum is itself Poisson-distributed. We adopted such a restriction in our models. Note the positive mass at 0 followed by a continuous tail on $\mathbb{R}_+$.

Effects of COVID-19

HD Charge surveys were completed between May 2020 and June 2022. To check for influences of the COVID-19 pandemic, we used case data as provided by the University of Oxford government response tracker [1]. In particular, we computed the average rate of change in confirmed US COVID-19 cases over the time interval relevant to each survey response. The result was treated as a crude measure of COVID-19 severity and included in model (1) by adding an appropriate term:

$$\log\left(\mathrm{E}\left[Y_{dtc}\right]\right) = \ldots + \gamma \times S_c.$$

For example, an estimated effect of $\hat{\gamma} = 0$ would suggest that the pandemic had little effect on spending. The results from figure 2 use this adjustment to probe a counterfactual world in which S_c is artificially set to 0.

Conclusions and Future Work

Out-of-pocket costs associated with HD are significant for PwHD's and their companions, and underscore the limited support available to affected individuals. **We estimated that both early- and middle-stage dyads spend over $5,000 USD annually** across the categories listed in table 1. Disease progression led to a significant increase in costs. **Late-stage dyads were estimated to spend nearly 300% more than earlier stages, totalling over $16,000 USD annually**. The categories associated with the highest spending were food delivery, medical care, and home maintenance; companions were estimated to spend roughly 30% more than PwHD's in general. Finally, the COVID-19 parameter γ was not found to differ significantly from 0.

Next steps towards our burden-of-illness model are manifold. We aim to incorporate other indirect costs (such as lost wages and opportunity cost), as well as direct costs from insurance claims data. We also plan to explore more sophisticated models with interaction terms. One expects disease stage to interact with spending categories, for example. It could also be that COVID-19 affected individual expenditure categories despite the null main effect.

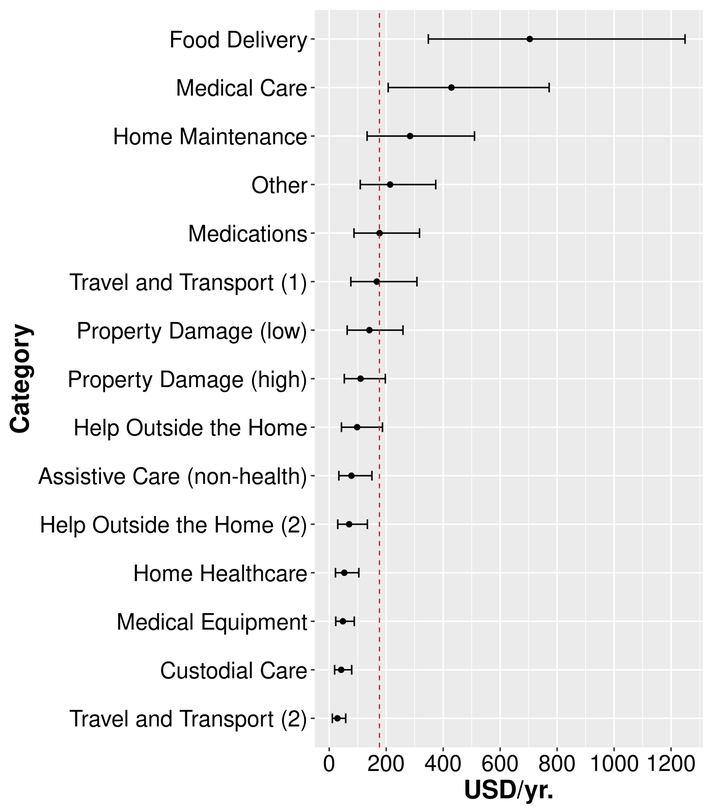

Figure 2: Cost estimates across 15 categories. Means from parametric bootstrap distributions are denoted as points within a 95% CI and the red line denotes the mean cost across all categories. Baseline is defined to be an early-stage PwHD. Advancing to middle stage was not found to significantly alter costs (CI: -56% to +76%), advancing to late stage increased costs by an estimated 298% (CI: +29% to +595%), and companions spent more than PwHD's by an estimated 27% (CI: 0% to +57%). There was no evidence for a significant COVID effect (CI: -.10 to .19). The results in the main text are found by forming appropriate parameter combinations and averaging over each bootstrap sample.

References

[1] Thomas Hale et al. "A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker)". In: *Nature Human Behaviour* 5.4 (2021), pp. 529–538. DOI: 10.1038/s41562-021-01079-8. URL: https://doi.org/10.1038/s41562-021-01079-8.

[2] Bent Jorgensen. "Exponential Dispersion Models". In: *Journal of the Royal Statistical Society. Series B (Methodological)* 49.2 (1987), pp. 127–162. ISSN: 00359246. URL: http://www.jstor.org/stable/2345415 (visited on 10/10/2023).

[3] I Shoulson et al. "Huntington disease: clinical care and evaluation." eng. In: *Neurology* 29.1 (Jan. 1979), pp. 1–3. ISSN: 0028-3878 (Print); 0028-3878 (Linking). DOI: 10.1212/wnl.29.1.1.

[4] Sarah J Tabrizi et al. "A biological classification of Huntington's disease: the Integrated Staging System". In: *The Lancet Neurology* 21.7 (2023/09/12 2022), pp. 632–644. DOI: 10.1016/S1474-4422(22)00120-X. URL: https://doi.org/10.1016/S1474-4422(22)00120-X.

[5] "Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group." eng. In: *Mov Disord* 11.2 (Mar. 1996), pp. 136–142. ISSN: 0885-3185 (Print); 0885-3185 (Linking). DOI: 10.1002/mds.870110204.

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