



## Risk mitigation behaviors to prevent infection in the mitochondrial disease community during the COVID-19 pandemic

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### ABSTRACT

**Background:** A challenge during the COVID-19 pandemic has been widespread adherence to risk-reducing behaviors. Individuals with mitochondrial disease (MtD) are special population with an increased risk of morbidity associated with infection.

**Purpose:** To measure risk mitigation behaviors (RMBs) in families affected by MtD and identify factors that may influence these behaviors.

**Methods:** An online questionnaire was distributed in April and June 2020. Individuals with MtD or their caregivers completed the survey.

**Results:** We received 529 eligible responses with  $n = 312$  completing all questions for our multivariate regression model. The most common RMBs were increased hand washing (96%), social distancing (94%), and avoiding public gatherings (93%). Higher numbers of recent healthcare visits ( $b = 0.62$ ,  $p < 0.05$ ) and expressed fear of the MtD patient contracting COVID-19 ( $b = 0.92$ ,  $p < 0.05$ ) were associated with more RMBs. Living in a rural community ( $b = -0.99$ ,  $p < 0.05$ ) and a history of COVID-19 testing ( $b = -2.14$ ,  $p < 0.01$ ) were associated with fewer RMBs.

**Conclusions:** Our results suggest that during the COVID-19 pandemic, families affected by MtD have near universal adherence to basic RMBs. This may be motivated by fear of the severe morbidity associated with infection in MtD. Patients with frequent healthcare visits may be sicker and therefore take more precautions. Living in a rural community may also impact these behaviors. People who practice fewer RMBs may be more likely to seek testing. Our findings may generalize to other chronic diseases.

### 1. Introduction

The COVID-19 pandemic has highlighted the importance of public health measures to mitigate the risk of infection [1,2]. Simple behavior modifications such as social distancing, mask wearing, and travel restrictions are proven effective methods to reduce the spread of SARS-COV-2, the virus that causes COVID-19 infection, in communities [1–4]. However, despite their effectiveness, there remains substantial resistance to these behavior changes throughout the United States [5,6].

For people with medical conditions that are associated with

increased vulnerability to infection, behaviors that mitigate the risk of exposure to viral pathogens are particularly important. People with mitochondrial disease (MtD) represent one such group at increased vulnerability [7]. Mitochondrial diseases are a group of clinically heterogeneous, multisystemic disorders caused by dysfunction of the energy producing organelle of the cell, the mitochondrion [8]. Metabolic decompensation is a major cause of morbidity, mortality and functional decline in patients with MtD. This rapid physiologic deterioration can be life threatening and is frequently triggered by acute infection [9]. Part of routine clinical counseling for patients with MtD is to avoid the

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precipitants of metabolic decompensation [8]. For this reason, families routinely employ strategies to avoid infection, particularly during cold and flu season. While this behavior is frequently discussed within the patient community through social media and advocacy groups and between providers in clinical consortiums, there have not yet been any formal studies to quantify this aspect of the patient experience.

In this context, we aimed 1) to quantify these *risk mitigation behaviors* (RMBs) in the MtD community as a special population with a vulnerability to infection and 2) to identify demographic, clinical and social characteristics that may influence these behaviors.

## 2. Methods

### 2.1. Survey design

A questionnaire (see Supplementary Material) was designed for this study by a panel of mitochondrial disease experts at our institution and members of the Scientific and Medical Advisory Board of the United Mitochondrial Disease Foundation (UMDF). No personal identifying data (name, phone number, address, email, etc.) was collected as part of the survey. Limited demographic information was obtained to maintain anonymity in this rare disease community. If a respondent had multiple family members affected by MtD in the household, the respondent was asked to complete the questionnaire once per household and answer questions for only the most affected family member. Respondents were able to skip any question to which they did not want to respond. Participation was entirely voluntary, and no compensation was offered by the study in exchange for responses. Prior to completing the questionnaire, a statement of eligibility and consent was required to be reviewed by the participants. If not verified, the survey automatically closed and was not available to be completed. Participants were also excluded if they responded that they had already taken the survey. The study was approved by the IRB and granted human subjects exemption by the Office of Human Subjects Research.

### 2.2. Study population

The target population was adults (>18 years old) with mitochondrial disease, as well as adult caregivers of adults or children with mitochondrial disease. Eligibility for these inclusion criteria was screened before survey completion as stated above. Questionnaires were completed in English through an online cloud-based software. The invitation to participate was distributed via an internet link through several mitochondrial disease advocacy groups (including, UMDF and People Against Leigh Syndrome (PALS)), as well as the North American Mitochondrial Disease Consortium (NAMDC), which is a member of the Rare Disease Clinical Research Network (RDCRN). The largest of these groups, the UMDF, has approximately 6000 recipients on its listserv with a 25% open rate and approximately 100 followers on social media with a 50% click rate. Based on a reported prevalence for MtD of 1 in 5000, this listserv is estimated to capture up to 10% of the families affected by MtD in the United States [10,11]. The survey was open and available for responses for a total of 8 weeks during April 2020 and June 2020.

### 2.3. Measures

To examine RMBs, respondents were asked to “check all that apply” to implementation of a list of seventeen different behaviors implemented since March 2020. This list was separated into three survey questions by the behavior domain: social (5 RMBs), shopping (4 RMBs) and hygiene behaviors (7 RMBs). Respondents could also select an “other” option in each category. The total number of selected RMBs (Total RMBs) out of a maximum 19 was used as a dependent variable for analysis.

To identify factors that may be associated with these behaviors,

additional survey questions were used as independent variables and categorized as follows: MtD characteristics, symptoms associated with COVID-19, recent healthcare system use, prior health behaviors, household characteristics, respondent identity (Supplementary material). Included in the MtD characteristics section of the survey was a list of comorbidities recognized by the Centers for Disease Control and Prevention (CDC) as risk factors for severe COVID-19 in April 2020 [12,13].

Questions that were formatted as “choose one” responses were analyzed as categorical variables. For questions that were formatted as “check all that apply”, responses were coded as counts of the total number of selected responses for that question and analyzed as count variables.

The final question of the survey included an open-ended write-in response to the question “What is your greatest concern regarding the COVID-19 pandemic?”. After qualitative review of these responses by the research team and quantitative analysis of common words by the survey software analytics tool, twelve themes were identified and themes expressed by greater than 5% of participants are reported. Responses for presence or absence of these themes were coded by two independent investigators. When there was disagreement between reviewers, a third investigator characterized the response independently to reach a consensus.

The most frequent response was fear that the affected family member would contract COVID-19 and this was added as an indicator variable to the analysis.

### 2.4. Statistical analyses

In our preliminary evaluation, the distribution of responses to the individual RMB questions appeared to discriminate between having none versus having any change as a result to COVID-19. Thus, we dichotomized these variables accordingly (reference category = no change). To construct our dependent RMB variables, we aggregated each dichotomous response option into a sum of changes for each variable (with zero equaling no-changes, 1 = one change, 2 = two changes, etc. up to the number of response options for each constructed count variable).

The dependent variables were analyzed using a truncated linear regression model, which is appropriate when the linear outcome variable is censored between some bounds as is the case with our constructed count variables [14,15]. Six variables (positive COVID-19 test, essential worker in the household, known exposure risk, fear of dying, fear of hospitalization and economic/financial concerns) were not included in the multivariate analysis for lack of explanatory power.

## 3. Results

### 3.1. Survey response

Overall, 529 individuals responded to the survey; 250 (47%) identified as a person with MtD, 240 (45%) identified as a caregiver of a person with MtD and 39 (7%) identified as both a person with MtD and a caregiver of a person with MtD

After casewise deletion of respondents with missing data, the effective sample size for our multivariate regression model (number of respondents who completed all questions for variables used in the model) was 312 respondents. For the sample used in the model, 141 (44%) identified as a person with MtD, 203 (64%) identified as a caregiver of a person with MtD and 25 (8%) identified as both a person with MtD and a caregiver of a person with MtD.

### 3.2. Demographics and clinical characteristics

The demographics and clinical characteristics of the individuals with MtD and their households are reported in [Table 1](#)

**Table 1**  
Characteristics of respondents and patients with MtD.

	n or [mean]	N***	% or [SD]
<b>Clinical characteristics of patients with MtD</b>			
Pediatric (Age < 18)	158	529	29.9
Adult (Age ≥18, <65)	317	529	59.9
Elderly (Age > 65)	54	529	10.0
Pathogenic variant identified	318	510	62.3
Received flu shot in 2019	357	516	69.1
Comorbidity count	[1.72]	312	[1.76]
Recent visit to healthcare setting count	[0.66]	529	[0.70]
Recent hospitalization count	[0.10]	529	[0.31]
Recent symptoms that overlap with COVID-19 count	[0.51]	312	[0.91]
History of COVID-19 testing	94	508	18.5
Positive COVID-19 test*	3	508	<1
<b>Household characteristics</b>			
2 or more people with MtD in household	102	529	19.3
Essential worker in the household*	181	493	36.7
<b>Community type</b>			
Rural	115	527	21.8
Suburban	328	527	62.2
Urban	84	527	15.9
American (United States)	499	529	94.3
International	30	529	5.7
<b>Expressed concerns regarding COVID-19 pandemic**</b>			
Fear of MtD patient contracting COVID-19	128	529	24.2
Known exposure risk*	68	529	12.9
Fear of dying*	66	529	12.5
Fear of hospitalization*	41	529	7.8
Economic/Financial concerns*	33	529	6.2

\* Not included in multivariate analysis for lack of explanatory power.

\*\* Concerns expressed by respondent.

\*\*\* Total available responses.

Regarding MtD subtype, the most common types of MtD reported in this cohort were mitochondrial disease not otherwise specified (33%), mitochondrial myopathy (28%), Leigh Syndrome (11%), Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) (8%), Chronic Progressive External Ophthalmoplegia (7%), polymerase gamma (POLG) Related Disorder (4%), and Kearns-Sayre syndrome (KSS) (3%). All other MtD subtypes represented less than 3% of the cohort and the complete distribution is included in the Supplementary

Material. Based on the distribution of types of MtD, this sample is similar to and representative of other reported registries of MtD patients [16].

### 3.3. Expressed concerns

In response to the question, “What is your greatest concern regarding the COVID-19 pandemic?”, the most common themes expressed were fear of the MtD patient contracting COVID-19, anxiety due to known exposure risk (e.g. a family member who works in a nursing home), fear of dying, fear of hospitalization and economic/financial concerns (Table 1).

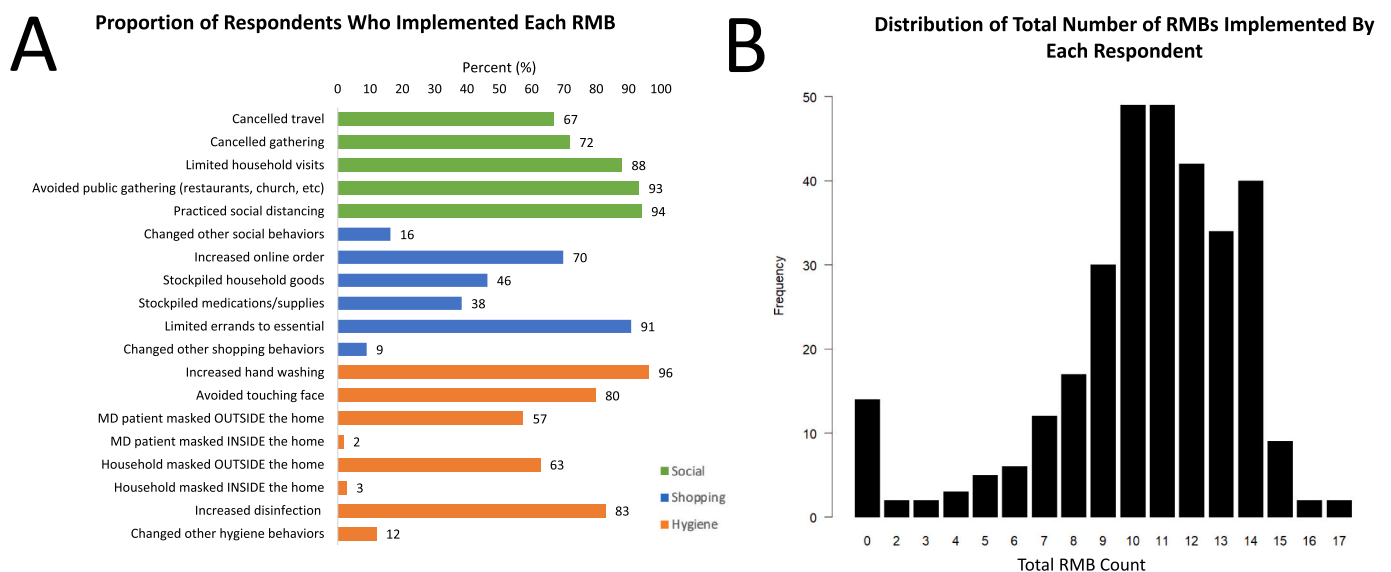
### 3.4. Risk mitigation behaviors

The distribution of total RMB counts ranged from 0 to 17 with a median of 10 and a mean of 9. Only 14 respondents (2.9%) reported zero RMBs. The frequency of each RMB as reported by respondents and the distribution of total RMB counts are illustrated in Fig. 1. The RMBs with the highest frequencies were increasing hand washing (96%), social distancing (94%), and avoidance of public gatherings (93%). The RMBs with the lowest frequencies were household members wearing masks inside the home (3%) and having the individual with MtD wear a mask inside the home (2%).

**Table 2**  
Factors associated with total RMBs from tobit regression results.\*

Factor	Effect Total RMBs	Statistical significance*
Higher number recent healthcare visits	↑	b = 0.62 p < 0.05
Fear of MtD patient contracting COVID-19	↑	b = 0.92 p < 0.05
Living in a rural community (versus urban, suburban)	↓	b = -0.99 p < 0.05
History of COVID-19 testing	↓	b = -2.14 p < 0.01

\* Adjusted model results with controls



**Fig. 1.** Legend: Panel A illustrates the percentage of respondents who implemented each RMB. Bars are color coded by RMB category: orange indicates hygiene behaviors (N = 491 responses), blue indicates shopping behaviors (N = 490 responses), and green indicates social behaviors (N = 490 responses). Panel B illustrates the distribution of total RMB counts for our model (N = 312 complete responses).

### 3.5. Factors associated with risk mitigation behavior

Based on our truncated multivariate regression model, three factors were identified as associated with the total RMBs— the number of recent healthcare visits, the community in which an individual with MtD lives, and history of testing for COVID-19, regardless of the test result (Table 2). Additionally, those who expressed fear that the patient with MtD will contract COVID-19 as their greatest concern had higher total RMB counts than those who did not (Table 2). The other variables listed in Table 1, as well as the identity of the respondent (MtD patient versus caregiver versus both) were not associated with the total number of RMBs in our model (Supplementary Material). Chi-square tests of the contingency table between exclusion/inclusion in the analysis and each background characteristic available in the final model revealed no significant differences between exclusion and inclusion (all p-values were greater than or equal to 0.1).

## 4. Discussion

Families affected by MtD employ a variety of strategies to decrease the risk of infection, with very high rates of compliance to some methods. During COVID, nearly all families reported adherence to basic principles of hand hygiene and social distancing. To compare our findings to other published data, we identified several studies conducted in the United State and internationally about health-related behaviors during the COVID-19 pandemic, and also other pandemics and epidemics in the last several decades, such as the H1N1 influenza pandemic. These studies reported on health behaviors and attitudes in the general population, but we did not identify similar studies that examined a special population affected by chronic disease. In comparison to two large studies of the general population during a similar period of the COVID-19 pandemic (including 979 and 3000 Americans), the rates of RMBs in the mitochondrial disease community are higher [17,18]. For example, 96% of members of the MtD community reported increased hand washing compared to 85% of the general public and 93% of members of the MtD community reported avoiding public gatherings compared to 77% of the general public [17]. These are exceptionally high adherence rates, particularly when compared to the 2009 H1N1 influenza pandemic, where for example, handwashing ranged from 53 to 89% and social distancing ranged from 11 to 69% [19,20]. These high rates are likely due to the understanding by the MtD community that infection may have more severe consequences for a patient with MtD than for the general population and thus they more frequently adhere to RMBs. This exceptional adherence rate may make the MtD community an excellent population to study the impact of near ideal adherence to behavioral modifications on health and physiology. The MtD population therefore may also represent a model system to understand strategies that translate more generally to other at-risk populations, such as others with pre-existing conditions, the elderly, and racial and ethnic minorities.

In our study, we identified several clinical factors that are associated with the total number of RMBs implemented in a household. Higher numbers of recent healthcare visits were associated with a higher number of RMBs. This behavior could be explained by the fact that patients with more frequent healthcare visits are likely to have more severe manifestations of the MtD and therefore, families with severely sick probands employed more behavioral modifications to try to protect the MtD patients. It is also possible that families recognize the high risk for exposure to infection in healthcare settings and therefore they have instituted more RMBs as COVID-19 preventative reactions to the healthcare visits. Some literature has termed this finding that recent illness influences health related behaviors as the “behavioral immune system.” [21] One such study using an online survey of over 1000 adults in the United States during the COVID-19 pandemic noted similar findings to ours, where recent illness was associated with more preventative health behaviors [22].

The geographic setting in which a person lives may also influence RMBs. In the MtD community, living in a rural setting was associated with fewer RMBs than living in an urban or suburban setting. This may be associated with a perceived decreased frequency of viral exposures in less dense living settings. Individuals in rural communities may therefore employ fewer RMBs as they feel their risk for exposure is lower in a rural setting. While this question has also been examined in prior literature, the data on which group is more adherent to preventative health behaviors is mixed with some studies finding rural communities to be more adherent, some to be less adherent, and some finding no relationship between this demographic and behavior [22–26]. As these studies have been conducted in diverse settings both within the United States and internationally, cultural differences may explain the discrepancy in findings. Of note, during the COVID-19 pandemic, the CDC has reported that rural communities have had lower rates of vaccination adherence and higher rates of vaccine hesitancy than urban communities [27]. Our data echoes this finding of reduced healthcare-related adherence in rural communities.

Prior history of testing for COVID-19 was associated with fewer RMBs, regardless of the test result. This suggests that individuals who sought out COVID-19 tests early-on in the pandemic may not have conformed to mitigation strategies as quickly as others. However, it should be recognized that at the time of this survey, COVID-19 testing was not universally available. While there exists some data regarding the relationship between *high-risk* behavior and testing for sexually transmitted diseases, there is insufficient data looking at the relationships with *risk-prevention* behavior and testing for respiratory infections [28,29]. One aforementioned study of 3000 Americans during the COVID-19 pandemic examined both preventative behaviors and testing, but did not examine the association between the two [18]. We may speculate that our findings could imply that people who practice fewer behaviors feel less secure and therefore seeks testing or, alternatively, that those who are tested feel a sense of security from testing and therefore practice fewer RMBs. Further studies are needed to elucidate those potential relationships.

Our finding that those respondents who expressed fear of the patient with MtD contracting COVID-19 had more RMBs supports the notion that the motivation behind high RMB adherence rates is fear of the consequences of infection for patients with MtD. While these particular fears are heightened in this community because of their potential neurologic vulnerability, the concept of fear or anxiety as a motivator for health-related behavior is not new. Several other studies surveying the general public support this correlation between fear of infection and increased preventative health behaviors [22,26,30]. In the US, a survey of 1019 adults found an association between germ aversion and preventative health behaviors early in the COVID-19 pandemic. Internationally during the same period, a study of over 15,000 Germans found that COVID-19-related fear predicted safety behavior and another study of over 800 Croatians found that germ aversion and belief in a second wave predicted adherence to similar behaviors [26,30]. However, what makes the MtD community exceptional is the high degree of adherence as a result of that anxiety. Further studies across different chronic disease communities could examine whether the potential severity of health-related consequences of infection dictates both the emotional and behavioral responses of patients.

While the other clinical factors examined in this study were not significantly associated with RMB counts, it is unclear whether in this community, our sample was too small to identify other relationships, or, whether this may be an idiosyncratic characteristic of this special population. For example, in the study mentioned above by Shook et al. of health behaviors during the COVID-19 pandemic, younger age was associated with increased infection prevention behaviors [22].

While this study was conducted specifically in the mitochondrial disease community, these principles may generalize to other communities for chronic diseases, particularly those with other inborn errors of metabolism and neurodevelopmental disabilities. Further research with

patient registries for more common conditions such as cerebral palsy and autism may better elucidate health behaviors in these larger communities.

Limitations of this study include that this questionnaire was reliant on self-report, which included the confirmatory diagnosis of MtD itself. While self-report measures are frequently and reliably used in both medical and social sciences literature, there exists the possibility of recall bias or dishonesty by self-report. Participants were also not required to complete all questions and may have intentionally or unintentionally, skipped or incompletely responded to one or more questions, leading to an underestimate of responses. Additionally, in order to capture the broad scope of MtD across the lifespan, both pediatric and adult populations were included, which required that our respondents were a mix of patients themselves and caregivers responding on the patient's behalf. This methodology has been used in other diseases where presentation occurs across the age-spectrum, such as sickle cell disease, cerebral palsy, autism and encephalitis [31–35]. While the identity of the respondent was controlled for in our model and not found to be a significant predictor of RMBs, it is possible that in a larger or different sample, patients themselves may answer differently than their caregivers [36]. Alternatively it is worth considering that RMBs may reflect the behavior of households rather than the behavior of individuals and therefore the identity of the respondent does not influence household behavior. This may be corroborated by our finding that the number of affected individuals in the household also did not influence RMBs.

Another limitation is that the survey was administered on an online platform and therefore our sample may be biased toward a higher socioeconomic status by excluding people without internet access. It was also only administered in the English language, excluding non-English speaking communities which are not represented here. The advocacy groups that distributed this questionnaire were also based in the United States and therefore primarily American families responded. As stated in the Methods section above, these advocacy groups also only represent approximately 10% of the estimated MtD population in the United States and our sample represents an even smaller portion. While our sample is descriptively similar to other published registries of MtD, different behavioral practices may be observed in communities affected by MtD that did not have access to or chose not to respond to this survey.

Finally, an additional consideration is that this study was completed during the initial peak of the COVID-19 pandemic in spring 2020 and prior to the introduction of effective vaccines. These behaviors therefore may represent higher rates of adherence than normal circumstances given the initial abundant fears and lack of understanding of the virus. It is possible that people with mitochondrial disease may have lower RMBs counts later in the pandemic, after the introduction of vaccines or after the pandemic ends. “Coronavirus burnout” and “pandemic fatigue” have also been described [37]. Alternatively, the COVID-19 pandemic may have proven to this population the effectiveness of certain behaviors to prevent infection such as mask wearing in public and adherence may persist. Indeed, a decline in other circulating respiratory viruses has been observed in the 2020–2021 season [38]. Follow up studies after the peak of COVID-19 pandemic will be needed to understand the long-term effects of the pandemic on behaviors of this population.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2021.100837>.

## References

- [1] D.K. Chu, E.A. Akl, S. Duda, et al., Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis, *Lancet* 395 (10242) (2020) 1973–1987.
- [2] B. Nussbaumer-Streit, V. Mayr, A.I. Dobrescu, Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review, *Cochrane Database Syst. Rev.* 9 (2020), CD013574.
- [3] J. Burns, A. Movsisyan, J.M. Stratil, International travel-related control measures to contain the COVID-19 pandemic: a rapid review, *Cochrane Database Syst. Rev.* 3 (2021), CD013717.
- [4] R. West, S. Michie, G.J. Rubin, R. Amlôt, Applying principles of behaviour change to reduce SARS-CoV-2 transmission, *Nat. Hum. Behav.* 4 (5) (2020) 451–459.
- [5] Hung Y-W. A Study of Barriers to the Wearing of Face Masks by Adults in the US to Prevent the Spread of Influenza.; 2018.
- [6] M.H. Haischer, R. Beilfuss, M.R. Hart, et al., Who is wearing a mask? Gender-, age-, and location-related differences during the COVID-19 pandemic, *PLOS ONE*. 15 (10) (2020), e0240785, <https://doi.org/10.1371/journal.pone.0240785>.
- [7] S.K. Kruk, S.E. Pacheco, M.K. Koenig, J.R.E. Bergerson, E. Gordon-Lipkin, P. J. McGuire, Vulnerability of pediatric patients with mitochondrial disease to vaccine-preventable diseases, *J. Allergy Clin. Immunol. Pract.* 7 (7) (2019) 2415–2418.e3.
- [8] S. Parikh, A. Goldstein, M.K. Koenig, et al., Diagnosis and management of mitochondrial disease: a consensus statement from the mitochondrial medicine society, *Genet. Med.* 17 (9) (2015) 689–701.
- [9] S. Eom, H.N. Lee, S. Lee, et al., Cause of death in children with mitochondrial diseases, *Pediatr. Neurol.* 66 (2017) 82–88, <https://doi.org/10.1016/j.pediatrneurol.2016.10.006>.
- [10] A. Schaefer, A. Lim, G. Gorman, Epidemiology of mitochondrial disease, in: M. Mancuso, T. Klopstock (Eds.), *Diagnosis and Management of Mitochondrial Disorders*, Springer International Publishing, 2019, pp. 63–79.
- [11] G.S. Gorman, A.M. Schaefer, Y. Ng, et al., Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease, *Ann. Neurol.* 77 (5) (2015) 753–759.
- [12] McMichael TM, D.W. Currie, S. Clark, Epidemiology of Covid-19 in a long-term care facility in King County, Washington, *New Engl. J. Med.* 382 (21) (2020) 2005–2011, <https://doi.org/10.1056/nejmoa2005412>.
- [13] CDC. COVID-19 and Your Health. Published May 13, 2021. Accessed June 2, 2021. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>.
- [14] W.H. Greene, *Econometric Analysis*, Prentice Hall, 2008.
- [15] J. Tobin, Estimation of relationships for limited dependent variables, *Econometrica* 26 (1) (1958) 24, <https://doi.org/10.2307/1907382>.
- [16] E. Barca, Y. Long, V. Cooley, et al., Mitochondrial diseases in North America: an analysis of the NAMDC registry, *Neurol. Genet.* 6 (2) (2020), e402.
- [17] S.K. Gadian, S.W. Goodman, T.B. Pepinsky, Partisanship, health behavior, and policy attitudes in the early stages of the COVID-19 pandemic, *PLoS One*. 16 (4) (2021), e0249596.
- [18] S. Li, B. Feng, W. Liao, W. Pan, Internet use, risk awareness, and demographic characteristics associated with engagement in preventive behaviors and testing: cross-sectional survey on COVID-19 in the United States, *J. Med. Internet Res.* 22 (6) (2020), e19782.
- [19] M. Bults, D.J.M.A. Beaujean, J.H. Richardus, H.A.C.M. Voeten, Perceptions and behavioral responses of the general public during the 2009 influenza A (H1N1) pandemic: a systematic review, *Disaster Med. Public Health Prep.* 9 (2) (2015) 207–219.
- [20] G.K. SteelFisher, R.J. Blendon, J.R.M. Ward, R. Rapoport, E.B. Kahn, K.S. Kohl, Public response to the 2009 influenza A H1N1 pandemic: a polling study in five countries, *Lancet Infect. Dis.* 12 (11) (2012) 845–850.
- [21] S.L. Miller, J.K. Maner, Sick body, vigilant mind: the biological immune system activates the behavioral immune system, *Psychol. Sci.* 22 (12) (2011) 1467–1471.
- [22] N.J. Shook, B. Sevi, J. Lee, B. Oosterhoff, H.N. Fitzgerald, Disease avoidance in the time of COVID-19: the behavioral immune system is associated with concern and preventative health behaviors, *PLoS One*. 15 (8) (2020), e0238015.
- [23] X. Chen, H. Chen, Differences in preventive behaviors of COVID-19 between urban and rural residents: lessons learned from a cross-sectional study in China, *Int. J. Environ. Res. Public Health* 17 (12) (2020) 4437, <https://doi.org/10.3390/ijerph17124437>.
- [24] M.M. Endrich, P.R. Blank, T.D. Szucs, Influenza vaccination uptake and socioeconomic determinants in 11 European countries, *Vaccine* 27 (30) (2009) 4018–4024.
- [25] A. Bish, S. Michie, Demographic and attitudinal determinants of protective behaviours during a pandemic: a review, *Br. J. Health Psychol.* 15 (Pt 4) (2010) 797–824.

- [26] B. Weismüller, A. Schweda, N. Dörrie, et al., Different correlates of COVID-19-related adherent and dysfunctional safety behavior, *Front. Public Health* 8 (2020), 625664.
- [27] B.P. Murthy, N. Sterrett, D. Weller, et al., Disparities in COVID-19 vaccination coverage between urban and rural counties — United States, december 14, 2020–April 10, 2021, *MMWR Morb. Mortal. Wkly Rep.* 70 (20) (2021) 759–764, <https://doi.org/10.15585/mmwr.mm7020e3>.
- [28] A.L. Wirtz, *The Global HIV Epidemics Among Men Who Have Sex with Men*, World Bank Publications, 2011.
- [29] J. Taveras, M.J. Trepka, P. Madhivanan, E.L. Gollub, J.G. Dévieux, B. Ibrahimou, HIV risk and testing behaviors among pregnant women tested for HIV in Florida by site type, 2012, *Women Health.* 59 (7) (2019) 815–827.
- [30] I. Hromatko, M. Tonković, A. Vranic, Trust in Science, perceived vulnerability to disease, and adherence to pharmacological and non-pharmacological COVID-19 recommendations, *Front. Psychol.* 12 (2021), 664554.
- [31] A.K. Yeshokumar, R.A. Blum, T. Randell, N. Jetté, A. Easton, Exploration of patient- and relative-reported outcomes of cognitive, emotional, and social function after encephalitis, *Brain Inj.* 35 (2) (2021) 255–263.
- [32] A.K. Yeshokumar, E. Gordon-Lipkin, A. Arenivas, et al., Neurobehavioral outcomes in autoimmune encephalitis, *J. Neuroimmunol.* 312 (2017) 8–14.
- [33] E. Gordon-Lipkin, A.K. Yeshokumar, D. Saylor, A. Arenivas, J.C. Probasco, Comparative outcomes in children and adults with anti- N-methyl-D-aspartate (anti-NMDA) receptor encephalitis, *J. Child Neurol.* 32 (11) (2017) 930–935.
- [34] R.K. Sandercock, E.M. Lamarche, M.R. Klinger, L.G. Klinger, Assessing the convergence of self-report and informant measures for adults with autism spectrum disorder, *Autism* 24 (8) (2020) 2256–2268.
- [35] A. Blake, N. Guthrie-Dixon, M. Grindley, A. Barton-Gooden, J. Knight-Madden, M. Asnani, Level of agreement between adolescents' self-assessment and parent proxy report of health-related quality of life in adolescents with sickle cell disease, *Pediatr. Blood Cancer* 67 (4) (2020), <https://doi.org/10.1002/pbc.28198>.
- [36] M.C. Ferreira, N.R. Garcia, C.O.M. Prudente, M.F.M. Ribeiro, Quality of life of adolescents with cerebral palsy: agreement between self-report and caregiver's report\*, *Rev. Latino-Am. Enfermagem.* 28 (2020) <https://doi.org/10.1590/1518-8345.3928.3300>.
- [37] How to deal with Coronavirus burnout and pandemic fatigue. Accessed December 15, 2021. <https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/how-to-deal-with-coronavirus-burnout-and-pandemic-fatigue>.
- [38] Rambaud J, Dager S, Morin L, et al. Bronchiolitis Admissions to Intensive Care During COVID. *Pediatrics*. Published online March 17, 2021. doi:10.1542/peds.2021-050103.