Texas Heart Institute Journal

Clinical Investigation

Cardiovascular Outcomes in Patients With Mitochondrial Disease in the United States: A Propensity Score Analysis

Tran Nguyen, MD[1]; Talal Alzahrani, MD, MPH[1]; Joseph Krepp, MD[1]; Gurusher Panjrath, MD[1]

[1]Division of Cardiology, Department of Medicine, George Washington University, Washington, DC

Mitochondrial disease comprises a wide range of genetic disorders caused by mitochondrial dysfunction. Its rarity, however, has limited the ability to assess its effects on clinical outcomes. To evaluate this relationship, we collected data from the 2016 National Inpatient Sample, which includes data from >7 million hospital stays. We identified 705 patients (mean age, 22 ± 20.7 yr; 54.2% female; 67.4% white) whose records included the ICD-10-CM code E88.4. We also identified a propensity-matched cohort of 705 patients without mitochondrial disease to examine the effect of mitochondrial disease on major adverse cardiovascular events, including all-cause in-hospital death, cardiac arrest, and acute congestive heart failure.

Patients with mitochondrial disease were at significantly greater risk of major adverse cardiovascular events (odds ratio [OR]=2.42; 95% CI, 1.29–4.57; P=0.005), systolic heart failure (OR=2.37; 95% CI, 1.08–5.22; P=0.027), and all-cause in-hospital death (OR=14.22; 95% CI, 1.87–108.45; P<0.001).

These findings suggest that mitochondrial disease significantly increases the risk of inpatient major adverse cardiovascular events. ***(Tex Heart Inst J 2021;48(3):e207243)***

Citation:
Nguyen T, Alzahrani T, Krepp J, Panjrath G. Cardiovascular outcomes in patients with mitochondrial disease in the United States: a propensity score analysis. Tex Heart Inst J 2021;48(3):e207243. doi: 10.14503/THIJ-20-7243

Key words:
Cardiovascular diseases; cohort studies; heart failure, inpatients/statistics & numerical data; mitochondrial diseases; propensity score

Corresponding author:
Tran Nguyen, MD, Department of Medicine, George Washington University, 2150 Pennsylvania Ave. NW, 4th fl., Washington, DC 20037

E-mail:
tnguyennb@gmail.com

Mitochondrial disease (MD) comprises a group of clinically heterogeneous disorders caused by dysfunctional oxidative phosphorylation and subsequent cellular inability to meet energy demands.[1,2] Because 90% of the heart's energy requirement depends on mitochondrial ATP generation, mitochondria play a key role in cardiovascular (CV) function in both healthy and diseased states.[2,3] Given this relationship, patients with MD presumably have increased rates of CV morbidity and mortality. Syndromes associated with MD include mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonic epilepsy with ragged red fibers; ataxia; chronic progressive external ophthalmoplegia; Kearns-Sayre syndrome; and sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.[4-7]

The general mechanism by which MD affects myocytes is mutation of mitochondrial proteins (either from mutation in mitochondrial or nuclear DNA, or through acquired defects). These mutations lead to defects in mitochondrial quality control, which initiates a vicious cycle of additional acquired mitochondrial defects and defects in metabolic signaling, calcium transport, bioenergetics, reactive oxygen species generation, and cell death pathway activation.[8-11]

A broad spectrum of cardiac complications has been linked to MD, ranging from cardiomyopathy (for example, hypertrophic remodeling, dilated cardiomyopathy, and heart failure [HF]) to electropathy (including conduction system disease and cardiac arrhythmia).[12-18] In one study, patients with the mitochondrial DNA mutation 3243A>G associated with MELAS showed echocardiographic evidence of left ventricular (LV) hypertrophy, which closely correlated with the degree of skeletal muscle mutant load in biopsy samples.[12] Cardiac biomarkers, such as atrial natriuretic factor and B-type natriuretic peptide, have also been closely linked to MD, specifically in patients with MELAS.[13] In addition, conduction defects, especially atrioventricular block, are an established characteristic of Kearns-Sayre syndrome.[14] Population studies have shown substantial effects that MD has on CV morbidity and mortality in pediatric patients with MD,

but confirming this in adults with MD has been limited by small sample sizes.[12,13,17-21] To fill this gap, we evaluated the relationship between MD and CV outcomes in a large sample of hospitalized patients in the United States.

Patients and Methods

Study Population

For this cross-sectional study, we searched the 2016 National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project, which includes data from >7 million hospital stays.[22] The NIS is the largest all-payer inpatient care database in the U.S. Patients assigned to code E88.4 (mitochondrial metabolism disorders) in the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) were categorized as having MD (n=705). The remaining patients were categorized as not having MD (n=7,132,963). Demographics, comorbidities, and risk factors commonly associated with adverse CV events were documented. These included hypertension, hyperlipidemia, obesity, history of stroke or percutaneous coronary intervention (PCI), chronic kidney disease, chronic HF, smoking, alcohol use, drug use, and hospitalization. Supplementary Table I presents the ICD-10-CM codes that we identified for each condition. No institutional review board approval was required for use of the NIS dataset.

Clinical Outcome Measures

The primary outcome was major adverse CV events (MACE), a composite endpoint including all-cause in-hospital death, cardiac arrest, and acute congestive HF. Other CV outcomes included all HF, acute HF, systolic HF, diastolic HF, cardiomyopathy, cardiac shock, PCI, cardioversion, pacemaker placement, implantable cardioverter-defibrillator treatment, atrial fibrillation/flutter, and supraventricular tachycardia. Secondary outcomes included acute kidney injury (AKI), sepsis, and ventilation.

Propensity Score Analysis

Baseline patient characteristics were used to assemble a propensity-matched cohort to examine the effect of MD on the incidence of MACE. This matched cohort (N=1,410) comprised 705 patients with MD and 705 patients without MD. This analysis was designed to balance observed covariates between the 2 groups and mimic the populations used in randomized studies.[23-25]

Statistical Analysis

The baseline demographic and clinical characteristics of patients with and without MD were compared by using χ^2 and Student *t* tests. The matched cohort was used to estimate the odds ratios (OR) for MACE and other clinical outcomes. The statistical analyses were performed using SAS 9.4 (SAS Institute Inc.). *P* values <0.05 were considered statistically significant.

Results

Baseline Characteristics

In total, 705 patients (0.01%) in the 2016 NIS dataset had a diagnosis of MD (Table I), giving an estimated prevalence of 10 per 100,000 individuals. The mean age of patients with MD was 22.2 ± 20.7 years; the group comprised slightly more women (54%) than men, and was predominantly white (67%). Table I lists the baseline demographic and clinical characteristics of all patients with or without MD (the unmatched cohort), as well as those of the matched cohort. Of note, in the unmatched cohort, patients with MD were generally younger than those without it (22.2 vs. 49.0 yr; *P* <0.001). Not surprisingly, given their older age, a larger proportion of patients without MD in the unmatched cohort had CV comorbidities, including type 2 diabetes, hypertension, hyperlipidemia, obesity, peripheral artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and pulmonary hypertension. They were also less likely to have undergone PCI or coronary artery bypass grafting. Nevertheless, after matching, we found no statistically significant differences in the baseline characteristics between the 2 groups.

Clinical Outcomes

In the matched cohort, the risk of MACE was higher in patients with MD (OR=2.42; 95% CI, 1.29–4.57; *P*=0.005), as was the risk of all-cause in-hospital death (OR=14.22; 95% CI, 1.87–108.45; *P* <0.001) (Table II and Fig. 1). Patients with MD were also at greater risk of cardiac arrest or acute congestive HF, although neither increase was statistically significant. Moreover, patients with MD were significantly more likely to have HF (OR=1.75; 95% CI, 1.01–3.03; *P*=0.043), systolic HF (OR=2.37; 95% CI, 1.08–5.22; *P*=0.027), and cardiomyopathy (OR=4.10; 95% CI, 2.10–8.01; *P* <0.001). However, there were no significant differences between groups in the rates of diastolic HF, cardiac shock, PCI, cardioversion, pacemaker placement, implantable cardioverter-defibrillator treatment, atrial fibrillation, atrial flutter, or supraventricular tachycardia.

In the analysis of secondary outcomes, patients with MD were at increased risk of AKI (OR=2.04; 95% CI, 1.27–3.28; *P*=0.003), sepsis (OR=8.33; 95% CI, 2.93–23.69; *P* <0.001), and undergoing mechanical ventilation (OR=6.40; 95% CI, 3.92–10.43; *P* <0.001) (Table II).

Discussion

To our knowledge, this is the first study to characterize the impact of MD on CV outcomes in a large sample of

TABLE I. Baseline Demographic and Clinical Characteristics of Patients in the Cohorts

	Unmatched (N=7,133,668)			**Matched** (N=1,410)		
Characteristic	**No MD** (n=7,132,963)	**MD** (n=705)	***P* Value**	**No MD** (n= 705)	**MD** (n=705)	***P* Value**
Age (yr)	49.0 ± 27.4	22.2 ± 20.7	<0.001	22.2 ± 20.6	22.2 ± 20.7	0.993
Female	4,044,446 (56.7)	383 (53.9)	0.133	383 (54.3)	382 (54.2)	0.957
Race/ethnicity						
White	4,425,353 (62.0)	479 (67.3)	0.004	475 (67.4)	475 (67.4)	0.999
Black	1,029,259 (14.4)	48 (6.7)	<0.001	48 (6.8)	48 (6.8)	0.999
Hispanic	830,116 (11.6)	109 (15.3)	0.002	107 (15.2)	107 (15.2)	0.999
Other	482,591 (6.8)	24 (3.4)	<0.001	24 (3.4)	24 (3.4)	0.999
Behavioral						
Smoking	951,694 (13.3)	24 (3.4)	<0.001	24 (3.4)	24 (3.4)	0.999
Alcohol use	363,755 (5.1)	3 (0.4)	<0.001	3 (0.4)	3 (0.4)	0.999
Drug use	399,265 (5.6)	24 (3.4)	0.01	28 (4.0)	24 (3.4)	0.52
Medical history						
Type 2 diabetes	1,478,142 (20.7)	63 (8.9)	<0.001	62 (8.8)	63 (8.9)	0.925
Hypertension	2,322,373 (32.6)	93 (13.1)	<0.001	93 (13.2)	93 (13.2)	0.999
Hyperlipidemia	1,873,092 (26.3)	63 (8.8)	<0.001	63 (8.9)	63 (8.9)	0.999
Obesity	897,361 (12.6)	54 (7.6)	<0.001	57 (8.1)	54 (7.7)	0.767
Cerebral infarction	127,658 (1.8)	10 (1.4)	0.439	6 (0.9)	10 (1.4)	0.315
Peripheral artery disease	218,694 (3.1)	6 (0.8)	<0.001	3 (0.4)	6 (0.9)	0.316
COPD	920,870 (12.9)	22 (3.1)	<0.001	28 (4.0)	22 (3.1)	0.388
CKD	955,924 (13.4)	41 (5.8)	<0.001	28 (4.0)	41 (5.8)	0.109
PAH	211,686 (3.0)	6 (0.8)	<0.001	10 (1.4)	6 (0.9)	0.315
CABG	275,740 (3.9)	5 (0.7)	<0.001	8 (1.1)	5 (0.7)	0.403
PCI	89,045 (3.9)	1 (0.8)	<0.001	8 (1.1)	6 (0.9)	0.591
Chronic heart failure	270,528 (3.8)	11 (1.5)	0.002	6 (0.9)	11 (1.6)	0.222
Depression	833,170 (11.7)	60 (8.4)	0.007	61 (8.7)	60 (8.5)	0.924
Anxiety	803,851 (11.3)	78 (11.1)	0.792	60 (8.5)	78 (11.1)	0.107
Hospital region						
Northeast	1,319,691 (18.5)	180 (25.3)	<0.001	527 (74.8)	527 (74.8)	0.999
Midwest	1,586,631 (22.2)	168 (23.6)	0.384	169 (24.0)	168 (23.8)	0.950
South	2,803,599 (39.3)	216 (30.3)	<0.001	214 (30.4)	214 (30.4)	0.999
West	1,424,457 (20.0)	148 (20.8)	0.584	144 (20.4)	145 (20.6)	0.947

CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MD = mitochondrial disease; PAH = pulmonary artery hypertension; PCI = percutaneous coronary intervention

Data are presented as mean ± SD or as number and percentage. $P<0.05$ was considered statistically significant.

inpatients. Our propensity analysis revealed a significant 2.4-fold higher risk (P=0.005) of MACE in patients with MD, suggesting that MD increases the risk of CV disease. Our results also revealed an increase in the risk of cardiac arrest and acute HF in patients with MD, although neither increase was significant. Our findings are consistent with increased in-hospital mortality rates observed by McCormack and colleagues[26] among approximately 2,000 hospitalized adult patients with MD, in a study using 2012 NIS data.

We noted an increased diagnostic prevalence of all HF, systolic HF, and cardiomyopathy among patients with MD when compared with the matched control group, consistent with findings in previous studies with smaller sample sizes.[14,17,18,20] Several molecular mechanisms have been evaluated as potential links between mitochondrial dysfunction and cardiomyopathy. As mentioned earlier, one proposed mechanism is dysregulation in apoptosis and eventual myocyte cell death.[10,11] Manifestations of mitochondrial cardiomyopathy vary

TABLE II. Clinical Outcomes in the Matched Cohort Based on the Presence of Mitochondrial Disease

Variable	No MD (n=705)	MD (n=705)	Odds Ratio (95% CI)	*P* Value
MACE	14 (2.0)	33 (4.7)	2.42 (1.29–4.57)	0.005
All-cause in-hospital death	1 (0.1)	14 (2.0)	14.22 (1.87–108.45)	<0.001
Cardiac arrest	2 (0.3)	6 (0.9)	3.02 (0.61–15.00)	0.156
Acute congestive heart failure	9 (1.3)	14 (2.0)	1.56 (0.67–3.64)	0.293
Other cardiovascular outcomes				
All heart failure	21 (3.0)	36 (5.1)	1.75 (1.01–3.03)	0.043
Acute heart failure	2 (0.3)	4 (0.6)	2.01 (0.36–10.99)	0.413
Systolic heart failure	9 (1.3)	21 (3.0)	2.37 (1.08–5.22)	0.027
Diastolic heart failure	11 (1.6)	10 (1.4)	0.90 (0.38–2.15)	0.826
Cardiomyopathy	11 (1.6)	43 (6.1)	4.10 (2.10–8.01)	<0.001
Cardiac shock	1 (0.1)	5 (0.7)	5.03 (0.59–43.15)	0.102
PCI	1 (0.1)	1 (0.1)	1 (0.06–16.02)	0.999
Cardioversion	1 (0.1)	2 (0.3)	2.00 (0.18–22.14)	0.563
Pacemaker placement	5 (0.7)	11 (1.6)	2.22 (0.77–6.42)	0.131
ICD placement	2 (0.3)	5 (0.7)	2.51 (0.49–12.98)	0.256
Atrial fibrillation/flutter	16 (2.3)	18 (2.6)	1.13 (0.57–2.23)	0.728
SVT	7 (1.0)	5 (0.7)	0.71 (0.23–2.25)	0.562
Secondary outcomes				
Acute kidney injury	27 (3.8)	53 (7.5)	2.04 (1.27–3.28)	0.003
Sepsis	4 (0.6)	32 (4.5)	8.33 (2.93–23.69)	<0.001
Ventilation	20 (2.8)	111 (15.7)	6.4 (3.92–10.43)	<0.001

ICD = implantable cardioverter-defibrillator; MACE = major adverse cardiovascular events; MD = mitochondrial disease; PCI = percutaneous coronary intervention; SVT = supraventricular tachycardia

Data are presented as number and percentage or as odds ratio and 95% CI. *P* <0.05 was considered statistically significant.

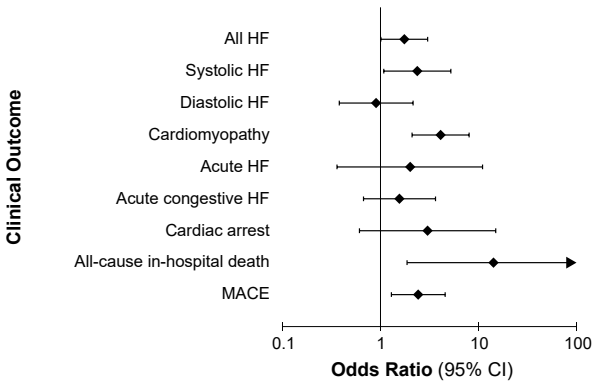

Fig. 1 *Forest plot shows the odds ratios for key clinical cardiovascular outcomes in patients with mitochondrial disease. Note especially the increased odds of all-cause in-hospital death and major adverse cardiovascular events (MACE).*

HF = heart failure

widely, from hypertrophic and dilated cardiomyopathy to LV noncompaction.[15,27-29] Hypertrophic remodeling is the most prominent pattern of cardiomyopathy in all forms of MD, the effects of which can mimic hypertrophic cardiomyopathy.[17,18] Left ventricular noncompaction, also called LV hypertrabeculation, is another recognized cardiac manifestation of MD.[30-32]

Our study corroborates the established association between MD, HF, and cardiomyopathy. Of note, our data also showed a significantly increased risk of sepsis and the need for mechanical ventilation therapy among patients with MD, which may be related to mitochondrial crisis. Patients with MD are at higher risk of metabolic crisis, which is often precipitated by infection or surgery.

Our study has several strengths. First, its large sample size enabled us to characterize MD, a relatively rare and likely underdiagnosed condition, and to provide a robust prevalence estimate (10 per 100,000 individuals). Our estimate, based on an inpatient database, was higher than previous estimates of 3 to 6.5 per 100,000 individuals from epidemiologic studies.[33-35] However, our study did not face certain challenges encountered in epidemiologic studies, such as the expanding number of genotypes and phenotypes and the ethical dilemma of performing invasive diagnostic tests (for example, muscle biopsy) on asymptomatic patients. Second, given that MD diagnosis can be missed, our findings can remind cardiologists about the broad, yet occasionally

nonspecific, spectrum of CV disease presentations in patients with MD. Third, by using propensity score matching, we were able to adjust for the differences in baseline characteristics, thus limiting the number of possible confounders.

Limitations. Our study also has limitations. First, NIS is an inpatient, administrative database that relies on provider-reported diagnoses and interpretation by the medical reviewers assigning ICD codes to them. Second, NIS cannot be used to investigate long-term health effects in patients with MD, so our analysis may underestimate the true rate of CV complications. Third, because of MD's broad spectrum, we did not include some medical conditions that may be considered MDs, such as Kearns-Sayre syndrome (ICD-10-CM code H49.81), hereditary optic atrophy (H47.22), Leigh disease (G31.82), and mitochondrial myopathy (G71.3). Instead, to focus on the relationship between MD and MACE, we chose code E88.4 for MD. Fourth, this was a cross-sectional study, and despite the propensity score matching, confounding may have resulted from variables not included in the final logistic regression model.

Conclusion

Our study substantiates the increased risk of CV morbidity and mortality in patients with MD. Further research to study the correlation between subclassifications of MD and MACE and to design more targeted medical treatments for this patient population is warranted. Meanwhile, as recognition of MD and its CV effects grows, cardiologists should be vigilant for CV manifestations and worsening prognosis on hospitalization among patients who have MD.

Supplementary Material

A supplemental table for this article is available at 10.14503_THIJ-20-7243.s1.pdf.

Published: 12 August 2021

References

1. Elliott HR, Samuels DC, Eden JA, Relton CL, Chinnery PF. Pathogenic mitochondrial DNA mutations are common in the general population. Am J Hum Genet 2008;83(2):254-60.
2. Murphy E, Ardehali H, Balaban RS, DiLisa F, Dorn GW 2nd, Kitsis RN, et al. Mitochondrial function, biology, and role in disease: a scientific statement from the American Heart Association. Circ Res 2016;118(12):1960-91.
3. Bates MGD, Bourke JP, Giordano C, d'Amati G, Turnbull DM, Taylor RW. Cardiac involvement in mitochondrial DNA disease: clinical spectrum, diagnosis, and management. Eur Heart J 2012;33(24):3023-33.
4. Koopman WJH, Willems PHGM, Smeitink JAM. Monogenic mitochondrial disorders. N Engl J Med 2012;366(12):1132-41.
5. Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820(5):619-24.
6. Fukuhara N, Tokiguchi S, Shirakawa K, Tsubaki T. Myoclonus epilepsy associated with ragged-red fibres (mitochondrial abnormalities): disease entity or a syndrome? Light-and electron-microscopic studies of two cases and review of literature. J Neurol Sci 1980;47(1):117-33.
7. Lee HF, Lee HJ, Chi CS, Tsai CR, Chang TK, Wang CJ. The neurological evolution of Pearson syndrome: case report and literature review. Eur J Paediatr Neurol 2007;11(4):208-14.
8. Wallace DC. A mitochondrial bioenergetic etiology of disease. J Clin Invest 2013;123(4):1405-12.
9. Wallace DC. Bioenergetic origins of complexity and disease. Cold Spring Harb Symp Quant Biol 2011;76:1-16.
10. Hoppins S, Nunnari J. Cell Biology. Mitochondrial dynamics and apoptosis--the ER connection. Science 2012;337(6098):1052-4.
11. Whelan RS, Kaplinskiy V, Kitsis RN. Cell death in the pathogenesis of heart disease: mechanisms and significance. Annu Rev Physiol 2010;72:19-44.
12. Majamaa-Voltti K, Peuhkurinen K, Kortelainen ML, Hassinen IE, Majamaa K. Cardiac abnormalities in patients with mitochondrial DNA mutation 3243A>G. BMC Cardiovasc Disord 2002;2:12.
13. Hsu YR, Yogasundaram H, Parajuli N, Valtuille L, Sergi C, Oudit GY. MELAS syndrome and cardiomyopathy: linking mitochondrial function to heart failure pathogenesis. Heart Fail Rev 2016;21(1):103-16.
14. Limongelli G, Tome-Esteban M, Dejthevaporn C, Rahman S, Hanna MG, Elliott PM. Prevalence and natural history of heart disease in adults with primary mitochondrial respiratory chain disease. Eur J Heart Fail 2010;12(2):114-21.
15. Meyers DE, Basha HI, Koenig MK. Mitochondrial cardiomyopathy: pathophysiology, diagnosis, and management. Tex Heart Inst J 2013;40(4):385-94.
16. Holmgren D, Wahlander H, Eriksson BO, Oldfors A, Holme E, Tulinius M. Cardiomyopathy in children with mitochondrial disease: clinical course and cardiological findings. Eur Heart J 2003;24(3):280-8.
17. Hirano M, DiMauro S. Clinical features of mitochondrial myopathies and encephalomyopathies. In: Lane RJM, editor. Handbook of muscle disease. New York: Marcel Dekker Inc.; 1996. p. 479-504.
18. Sorajja P, Sweeney MG, Chalmers R, Sachdev B, Syrris P, Hanna M, et al. Cardiac abnormalities in patients with Leber's hereditary optic neuropathy. Heart 2003;89(7):791-2.
19. Vydt TCG, de Coo RFM, Soliman OII, Ten Cate FJ, van Geuns RJM, Vletter WB, et al. Cardiac involvement in adults with m.3243A>G MELAS gene mutation. Am J Cardiol 2007;99(2):264-9.
20. Anan R, Nakagawa M, Miyata M, Higuchi I, Nakao S, Suehara M, et al. Cardiac involvement in mitochondrial diseases: a study on 17 patients with documented mitochondrial DNA defects. Circulation 1995;91(4):955-61.
21. Wahbi K, Bougouin W, Behin A, Stojkovic T, Becane HM, Jardel C, et al. Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases. Eur Heart J 2015;36(42):2886-93.
22. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2016. Agency for Healthcare Research and Quality, Rockville, MD. Available from: www.hcup-us.ahrq.gov/nisoverview.jsp

23. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. J Educ Psychol 1974;66(5):688-701.
24. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70(1):41-55.
25. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci 2010;25(1):1-21.
26. McCormack SE, Xiao R, Kilbaugh TJ, Karlsson M, Ganetzky RD, Cunningham ZZ, et al. Hospitalizations for mitochondrial disease across the lifespan in the U.S. Mol Genet Metab 2017;121(2):119-26.
27. DiMauro S. Mitochondrial myopathies. Curr Opin Rheumatol 2006;18(6):636-41.
28. Wahbi K, Larue S, Jardel C, Meune C, Stojkovic T, Ziegler F, et al. Cardiac involvement is frequent in patients with the m.8344A>G mutation of mitochondrial DNA. Neurology 2010;74(8):674-7.
29. Seibel P, Degoul F, Bonne G, Romero N, Francois D, Paturneau-Jouas M, et al. Genetic biochemical and pathophysiological characterization of a familial mitochondrial encephalomyopathy (MERRF). J Neurol Sci 1991;105(2):217-24.
30. Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, et al. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? Eur Heart J 2008;29(1):89-95.
31. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000;36(2):493-500.
32. Finsterer J. Cardiogenetics, neurogenetics, and pathogenetics of left ventricular hypertrabeculation/noncompaction. Pediatr Cardiol 2009;30(5):659-81.
33. Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, et al. The epidemiology of pathogenic mitochondrial DNA mutations. Ann Neurol 2000;48(2):188-93.
34. Yu-Wai-Man P, Griffiths PG, Brown DT, Howell N, Turnbull DM, Chinnery PF. The epidemiology of Leber hereditary optic neuropathy in the North East of England [published erratum appears in Am J Hum Genet 2016;98(6):1271]. Am J Hum Genet 2003;72(2):333-9.
35. Majamaa K, Moilanen JS, Uimonen S, Remes AM, Salmela PI, Karppa M, et al. Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes: prevalence of the mutation in an adult population. Am J Hum Genet 1998;63(2):447-54.