Assessing the relationships of obesity, smoking, and MS genetic risk on MS disability

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BACKGROUND

Most prior research aimed at investigating factors influencing disability accumulation in multiple sclerosis (MS) has focused on the Expanded Disability Status Scale (EDSS), which is a modestly reliable tool. Far fewer studies have investigated other robust outcomes, much less multiple outcomes in the same population.

OBJECTIVE

To describe the relationships between established MS risk factors and MS disability, including the MS Severity Scale (MSSS; a global measure of disability derived from the EDSS and accounts for disease duration), Timed 25-Foot Walk (T25FW; a robust measure of lower limb disability), and Nine Hole Peg Test (9HPT; a robust measure of upper limb disability). The genetic and non-genetic risk factors of interest are *HLA-DRB1*15:01*, *HLA-A*02:01*, genetic risk score (GRS) based on 200 other putative risk variants, tobacco smoke, obesity, and lower socioeconomic status.

MATERIALS & METHODS

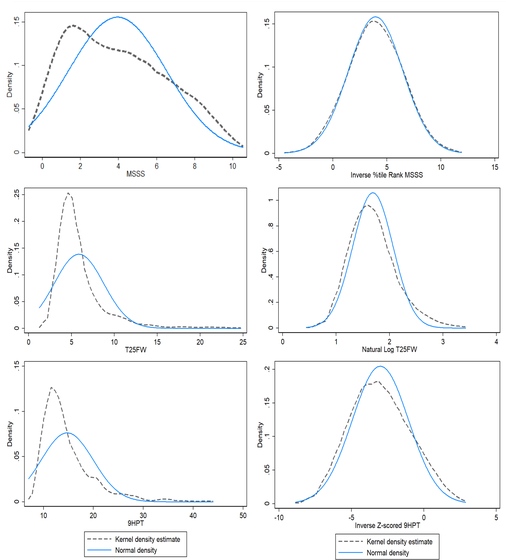
STUDY POPULATION. The study population consisted of participants in the Accelerated Cure Project for MS recruited from 10 MS specialty clinics across the United States (www.acceleratecure.org).

OUTCOMES. Participants completed an epidemiologic questionnaire administered by a clinician or trained personnel. Participants' most recent EDSS, T25FW, and 9HPT measures were extracted from their medical records. EDSS and disease duration were used to generate MSSS, which has a scale of 0 to 10. MSSS underwent an inverse percentile-rank transformation to meet normality (Figure 1). T25FW is the time needed walk 25 feet without assistance, and it underwent a natural logarithmic transformation. 9HPT is the average time to place nine pegs in nine holes for the dominant hand for two trials, repeated by the non-dominant hand. 9HPT underwent an inverse Z-score transformation[1].

PREDICTORS. Participants reported key demographics and year of education, which was used as a proxy for socioeconomic status. Ages of all start/stop periods of smoking tobacco or being obese were reported and were used to determine the participant's smoking and obesity status when the outcomes were measured. Also reported were detailed medical histories, including diversity of symptoms at onset which determined if the participant was polysymptomatic at onset, and time between first and second MS relapse. A subset of non-Hispanic white participants were genotyped on the Illumina Exome Core and iSelect platform for ~300,000 variants, including 200 putative non-major histocompatibility complex (MHC) risk variants[2]. *HLA-DRB1*15:01* and *HLA-A*02:01* were determined by tagging SNPs rs3135388 and rs2975033, respectively. The GRS was the sum of the risk alleles across the 200 non-MHC variants.

STATISTCAL ANALYSIS. Multivariable linear regression models to investigated the association between predictors of interest and each outcome. Disease duration was included as a predictor for the T25FW and 9HPT models. We excluded participants with disease duration <1 year from all models. Backward stepwise elimination was used for variable selection of non-genetic variables (α = 0.15). In the subset of the population with genetic data, each genetic variable was considered iteratively in the final non-genetic model, adjusting for population ancestry.

Figure 1: Distribution of the outcomes



1. Fischer JS, Rudick RA, Cutter GR and Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Multiple sclerosis.* 1999, 5: 244-50.
2. Patsopoulos N, Baranzini SE, Santaniello A, et al. The Multiple Sclerosis Genomic Map: Role of peripheral immune cells and resident microglia in susceptibility. bioRxiv. 2017.

Table 1: Population characteristics

Trait		MSSS	T25FW	9HPT
N		**646**	**553**	**354**
Age at exam (mean; SD)		45.0 (10.1)	44.2 (10.1)	44.7 (9.9)
Onset age (mean; SD)		32.7 (9.5)	33.0 (9.8)	32.8 (9.9)
Disease duration (mean; SD)		12.3 (9.3)	11.3 (9.2)	11.9 (9.6)
Male		23.5%	22.4%	21.8%
Primary progressive		7.7%	7.6%	5.9%
Race (%)	White	93.2%	96.2%	98%
	Black	5.9%	2.7%	1.4%
	Other	0.9%	1.1%	0.6%
Years of Education (mean; SD)		15.6 (2.9)	15.8 (2.9)	15.5 (2.9)
Obesity at exam (%)		12.3%	10.1%	13.0%
Smoking status at exam (%)	Never	48.2%	49%	43.0%
	Current	7.0%	7.6%	8.7%
	Former	44.8%	43.4%	48.3%
Polysymptomatic at onset (%)		57.7%	61.8%	64.1%
Time between 1st two relapses (years)	≤1	50.5%	50.1%	49.3%
	2-5	29.4%	29.8%	30.0%
	5+	20.1%	20.1%	20.7%
***HLA-DRB1*15:01* carriers** (%)		50.0%	45.3%	44.4%
***HLA-A*02* carriers** (%)		40.2%	40.7%	39.6%
GRS (mean; SD)		263.2 (8.9)	263.2 (8.6)	262.9 (8.9)
EDSS		3.1 (2.0)		
MSSS		3.9 (2.5)		
T25FW (seconds)			6.2	
9HPT (seconds)				15.2

Table 2: Linear regression associations

Trait		Inv %tile(MSSS)		Ln(T25FW)		Inv-z(9HPT)	
		β	p	β	p	β	p
Age at exam							
Onset age		**0.07**	$1.4x10^{-12}$	**0.007**	0.0016		
Disease duration				**0.014**	$4.7x10^{-11}$	**0.06**	$4x10^{-8}$
Male		**0.71**	0.00084			**1.34**	$2.3x10^{-8}$
Primary progressive		**1.59**	$1.5x10^{-5}$	**0.30**	$9x10^{-6}$	**1.04**	0.019
Race	White	Ref		Ref		Ref	
	Black	**1.40**	0.00026	0.17	0.11	**1.93**	0.021
	Other	-0.64	0.49	0.10	0.53	0.44	0.81
Years of Education		-0.06	0.056				
Obese at exam		**0.55**	0.041	0.09	0.11		
Smoking status at exam	Never			Ref		Ref	
	Current			**0.14**	0.045	**0.90**	0.013
	Former			0.02	0.62	-0.09	0.66
Polysymptomatic at onset		0.35	0.067				
Time between 1st two relapses (years)	≤1	Ref				Ref	
	2-5	**-0.48**	0.027			-0.25	0.28
	5+	**-1.33**	$6.9x10^{-8}$			**-1.26**	$5.6x10^{-6}$
HLA-DRB1*15:01 [1]		0.12	0.43	-0.055	0.06	-0.12	0.47
HLA-A*02 [2]		0.075	0.63	-0.027	0.33	-0.14	0.38
GRS [3]		0.017	0.16	0.000	0.83	0.003	0.78

1. *HLA-DRB1*15:01* sample size: MSSS=561, T25FW=496, 9HPT=331
2. *HLA-A*02:01* sample size: MSSS=561, T25FW=496 , 9HPT=331
3. GRS sample size: MSSS=478, T25FW=420 , 9HPT=281

RESULTS & CONCLUSIONS

MSSS Global disability was higher for participants who were older at MS onset, male, had primary progressive MS, and reported being obese (Table 2). Black participants had greater disability than white participants. Interestingly, individuals who had a longer interval between their first two relapses had lower disability.

T25FW Impairments in walking was greater for participants who were older at MS onset, longer disease duration, had primary progressive MS, and who were actively smoking.

9HPT Impairments in upper limb functionality/dexterity was greater for participants with a longer disease duration, who were male, had primary progressive MS, and who were actively smoking. Black participants had greater impairments than white participants. Lower impairments was associated with a longer interval between the first two relapses.

CONCLUSIONS.

1. MS genetic risk factors **DO NOT** influence MS disability – suggesting the processes contributing to risk differs.
2. As expected, older age of MS onset and longer disease duration were associated with greater disability
3. Male and Black participants also had greater disability than female and white participants, respectively.
4. Being obese impacted global disability and smokers had greater deficits in walking and dexterity.
5. Time between 1st two relapses might be an early indicators of long-term disability outcomes.