



Estimating the prevalence of cognition and mental health among multiple sclerosis patients: A population-based cross-sectional study



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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic neurological disease, considered most common autoimmune disorder of the central nervous system with dramatic impact on patient's emotional/mental well-being. Cognitive decline is acknowledged as debilitating symptom of MS. This paper aims to estimate the prevalence of cognition and mental health impairment among MS patients in Kuwait and test their association with socio-economic factors.

Methods: Data were collected from 224 MS patients. As scales of MS quality of life inventory (MSQOLI), mental health inventory (MHI) and perceived deficit questionnaire (PDQ) were used to estimate scores for mental health and cognition, respectively. Tertiles were used to estimate prevalence and associations were tested accordingly. **Results:** The prevalence of cognition and mental health impairment were approximately 23.3% and 14.1%, respectively. When stratified by gender, significant difference exists in mental health impairment. When stratified by nationality, there is significant difference between Kuwaiti and Non-Kuwaiti Arabs in cognition. Poorest patients had median cognition score worse than all other income categories.

Conclusion: MS in Kuwait seems to have an earlier age at onset. There is significant gender difference in mental health impairment among patients. Future interventions should be directed toward women, low-income, and non-Kuwaiti-Arabs. The estimated prevalence is based on self-reported data, tertiles as cut-off points, and hence should be interpreted with caution. PDQ and MHI are MSQOLI scales used as screening tools that don't correlate well with an objective test and shouldn't replace objective measures of physical and cognitive function tests including expanded disability status scale or magnetic resonance imaging.

1. Introduction

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system, affecting 1 in 1000 people in Western countries (Pugliatti et al., 2006). MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). Although the cause is unclear, the underlying mechanism is thought to be either destruction by the immune system or failure of the myelin-producing cells (Nakahara et al., 2013). As there is no cure for MS, treatment focuses instead on preventing new attacks or improving function after an attack occurs. The outcome of this disease depends on many factors. Of these factors, female gender, early age of onset, those who initially experienced few attacks and those with a relapsing course usually have better outcomes. Life expectancy is 5 to 10 years lower on average compared to unaffected population (Compston and Coles, 2008).

As a chronic disabling disease, MS has a dramatic impact on a person's emotional and mental wellbeing and as such, MS patients appear to have a higher prevalence of psychiatric symptoms (Chwastiak and Ehde, 2007). While these symptoms are not directly related to neurological impairment or disability, they are regarded by patients as being more important determinants of their overall health status than impaired physical function (Rothwell, 1998). The Multiple Sclerosis Quality of Life Inventory (MSQLI) is a commonly used instrument that can assess a wide array of impairments in MS patients, including cognition and mental health (Fischer et al., 1999; National MS Society, 2019). These measures are alternative indicators of the impact of the disease, particularly relevant in chronic conditions. Moreover, determining those elements that have an impact upon MS patient's mental status can help decision-makers in the planning of interventions, treatments and services.

Depression is the most important determinant of quality of life for

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MS patients (Skokou et al., 2012; Haussleiter et al., 2009; Siegert and Abernethy, 2005). However, it was not until the 1950s that empirical research on the frequency of depression among people with MS really began (Butler and Bennett, 2003). Life time prevalence of major depression in MS patients is as high as 50% (Schiffer, 1990). A study in Italy suggests that the annual prevalence of major depression in MS is elevated compared with that in both healthy people and those with other chronic conditions (Patten et al., 2003). In that study, a 12 month prevalence of 25.7% for major depression in people with MS in the 18–45 years is reported (Patten et al., 2003). Anxiety rates in the newly diagnosed MS cases are approximately 34% (Haussleiter et al., 2009). Another concern is that depression in people with MS is often not detected and treated (Butler and Bennett, 2003; Schiffer, 1990).

Many people who suffer from MS experience cognitive changes at some point during the disease. Cognitive problems usually develop in 40% to 65% of people with MS (Bobholz and Rao, 2003; McIntosh-Michaelis et al., 1991; Rao et al., 1991). Brain atrophy and the number of lesions as well as their areas on magnetic resonance imaging strongly correlate with cognitive function (Geurts et al., 2012). In a research conducted on 60 relapsing-remitting MS patients, it was noticed on their MRI that the volume of the hippocampus and thalamus were greatly reduced, which affected certain cognitive functions such as information processing (Debernard et al., 2015). Furthermore, MS patients with serious cognitive issues notice difficulties with problem-solving and planning where they usually become frustrated and overwhelmed when the task before them gets too complex. Other MS patients are sometimes unable to self-regulate their behavior which creates social problems (Haussleiter et al., 2009).

Kuwait is considered a high-risk area for MS (Alroughani et al., 2014; Al-Temaimi et al., 2015). According to data collected between October 2010 and April 2013 using the newly developed national MS registry in Kuwait, about 1176 MS patients were identified of which 927 (78.8%) were Kuwaitis and 249 (21.2%) were expatriates (Alroughani et al., 2014). During the study period, the prevalence and incidence rates of MS in Kuwait were 85.05 per 100,000 persons and 6.88 per 100,000 persons (Alroughani et al., 2014). Between 1990 and 2013, the prevalence of MS in Kuwait increased drastically from 4.4 per 100,000 persons in 1990 to 85.05 per 100,000 persons in 2013 (Alroughani et al., 2014; Al-Temaimi et al., 2015).

Despite the increasing number of MS patients in Kuwait and the Arabian Gulf region, there is a lack of research on cognition and mental health impairment regarding this population. Therefore, the goals of this study are to: estimate the prevalence of cognition and mental health impairment among MS patients using self-reported data and tertiles from scores for two scales of the MSQLI. The association between mental health and cognition was tested with an array of socio-demographic factors.

2. Methods

2.1. Study design and participants

A cross-sectional design in which data were collected by a non probability sample from 224 patients visiting Kuwait general hospitals (Al-Amiri, Mubarak Al-Kabeer, Iben Sena) using a self-administered structured questionnaire. Additionally, MS patients from Kuwait MS society were approached. Patients were reached in the departments of internal medicine, emergency medicine, and outpatient clinics. Patients older than 18 years were approached. Patients were excluded if they decline to participate in the study or if they were younger than 18 years. MS patients were given a questionnaire that contains 3 sections: socio-demographic information, cognition, and mental health.

2.2. Study instrument

The MSQLI is a battery consisting of 10 individual scales providing a

quality of life measure that is both generic and MS-specific (Fischer et al., 1999; National MS Society, 2019). The Perceived Deficits Questionnaire (PDQ) and Mental Health Inventory (MHI) are two of ten components (scales) of the MSQLI which is a modular MS-specific Health Related Quality of Life (HRQOL) instrument (Fischer et al., 1999). Cognition score was measured using the PDQ, whereas, mental health score was measured using the MHI. In the current study, PDQ and MHI are merely used as screening tools to estimate a score for PDQ and MHI and by no means they may replace a diagnosis by a neuroscientist. The reliability and construct validity of the MSQLI were rigorously evaluated in a field test with definite MS cases and a broad range of physical impairment (Fischer et al., 1999). There is good internal consistency reliability for the subscales of the MSQLI, with the lowest alpha being 0.67. Other coefficients range from 0.78 to 0.97. Good content validity for the MSQLI was ensured by the mode of development, which was designed to develop HRQOL measures specifically for MS patients (National MS Society, 2019).

The PDQ and MHI questionnaires were translated into Arabic and then back translated into English by two independent people and any differences were resolved through discussion. The whole instrument was pilot tested for understandability and cohesion and modifications were implemented as necessary. The time needed to complete the questionnaire was on average about 10 min. Each variable in the questionnaire was coded using a Likert scale, ranging from all the time (coded 1) to never (coded 6). To obtain a final score for each participant on each of cognition and mental health, a special scoring system is used by adding up the scores on 4 subscales. The cognition subscales were: attention/concentration, retrospective memory, prospective memory, planning/organization, and total perceived deficits. The mental health subscales were: total anxiety, total depression, total behavioral control, total positive effect, and total mental health index score.

2.3. Statistical analysis

Data were collected from 224 patients who attended either the Kuwaiti MS association events or during their visits to Al-Amiri, Mubarak Al-Kabeer, and Iben Sena hospitals. Of the patients, 62 were males and 161 females (one value missing). For skewed distributions the sample median was calculated to represent the center and inter-quartile-range (IQR) to represent variability compared to sample mean and standard deviation for symmetric distribution. The Mann–Whitney *U* (Kruskal–Wallis) test was used to compare medians of two (three) groups when the normality assumption (homogeneity of variances) fails. Probability value (PV) < 5% was considered statistically significant. Ethical approval was obtained from the ethics Committees at the Health Science Center in the Faculty of Medicine at Kuwait University and Kuwait Ministry of Health. Informed consents were provided to all participants.

3. Results

Table 1 shows that 86.1% of the patients were between 21 and 50 years old. The majority were Kuwaitis (76.3%), females (72.2%), and Non-Kuwaiti-Arabs (21.4%). Approximately 57.6% were married and 34.4% were single. About 67.9% had a bachelor degree, 25.5% had a high school or less, and 6.7% had post-graduate degree. About 51.8% of the participants were employed and 30.4% unemployed. About 32.6% have an income of 501–1000, or less than 500 (28.1%) KD/month. Most of the patients had no family history of neurological diseases (75.4%). About 83.0% were diagnosed at ages between 11 and 40 years old. Table 2 shows the total PD score which is the sum of four subscales of cognition: attention/concentration, retrospective memory, prospective memory, and planning/organization subscale. According to the PD questionnaire documentation that higher score is worse, the third tertile is considered as the estimate of the prevalence of cognition. Data revealed that 52 of 223 patients scored in the third tertile giving an

Table 1
Demographic characteristics of MS patients in Kuwait (N^a = 224).

Characteristic	n	%
Age ^a		
18–20	12	5.4
21–30	85	37.9
31–40	74	33.0
41–50	34	15.2
51–60	18	8.0
Gender ^a		
Male	62	27.8
Female	161	72.2
Nationality ^a		
Kuwaiti	171	76.3
Non-Kuwaiti Arabs	48	21.4
Non-Arabs	4	1.8
Marital status		
Single	77	34.4
Married	129	57.6
Divorced	14	6.3
Widowed	4	1.8
Level of education		
Primary school	6	2.7
High school	51	22.8
College/University	152	67.9
Higher Education	15	6.7
Occupation ^a		
Student	39	17.4
Employed	116	51.8
Unemployed	68	30.4
Monthly family income ^a		
Less than 500 ^b	63	28.1
501–1000	73	32.6
1001–1500	53	23.7
More than 1501	28	12.5
Family history		
Yes	55	24.6
No	169	75.4
Age at diagnosis		
0–10	15	6.7
11–20	64	28.6
21–30	78	34.8
31–40	44	19.6
41–50	22	9.8
51–60	1	0.4

^a Some values are missing.
^b 1 Kuwaiti Dinar = \$3.3 USA.

estimate of 23.3% for the prevalence of cognition with median score of 81 out of 100. Table 3 shows the total mental health index score which was calculated by averaging all questions in MHI minus 1 and dividing by 5 and then multiplying by 100. According to the MHI documentation that lower score is worse, the first tertile is considered as an estimate for the prevalence of mental health impairment. Data revealed that 31 out of 222 patients were in the first tertile giving a prevalence of 14.1% with median score of 23.33 out of 100. Table 4 shows the total PD score as well as total scores of four subscales of cognition: attention/concentration, retrospective memory, prospective memory, and planning/organization subscale. Table 4 compares the proportion and median score of cognition stratified by gender. According to the PD questionnaire documentation that higher score is worse, the third tertile is considered as an estimate for the prevalence of cognition. When comparing the prevalence of males (13.1%) to females (24.8%) on the prospective memory subscale, a border line significance is obtained (PV = 0.058). A closer look at total perceived cognition deficit reveals that there is no significant difference between males (19.7%) and the females (24.2%) (PV = 0.472). Table 5 presents the total MHI score as well as total scores of four subscales of mental health impairment: anxiety, depression, behavioral control, and positive affect. According to the MHI questionnaire the total score was calculated by averaging all the questions in MHI minus 1 and dividing by 5 and then multiplying by

Table 2
Prevalence of cognitive impairment, median score and IQR for MS patients in Kuwait (N = 224).

Cognitive subscales ^a	n ^d	%	Median	IQR
Attention/Concentration ^b				
1st Tertile	90	40.4%	4	6
2nd Tertile	79	35.4%	13	5
3rd Tertile	54	24.2%	20.5	2
Retrospective memory ^b				
1st Tertile	100	44.8%	4	5
2nd Tertile	63	28.3%	13	5
3rd Tertile	60	26.9%	20	2
Prospective memory ^b				
1st Tertile	110	49.3%	4	4
2nd Tertile	64	28.7%	13	4
3rd Tertile	49	22%	20	2
Planning/Organization ^b				
1st Tertile	113	50.7%	3	5
2nd Tertile	62	27.8%	12	5
3rd Tertile	48	21.5%	21	2
Total perceived deficits score ^c				
1st Tertile	103	46.2%	17	17
2nd Tertile	68	30.5%	50	18
3rd Tertile	52	23.3%	81	11

^a In cognition higher score is worse.
^b The score is out of 25.
^c The score is out of 100.
^d Some values are missing.

Table 3
Prevalence of mental health impairment, median score and IQR for MS patients in Kuwait (N = 224).

Mental health subscale ^a	n ^c	%	Median	IQR
Total anxiety subscale ^b				
1st Tertile	88	40%	28	12
2nd Tertile	83	37.7%	48	16
3rd Tertile	49	22.3%	80	18
Total depression subscale ^b				
1st Tertile	92	41.8%	15	20
2nd Tertile	79	35.9%	50	20
3rd Tertile	46	22.3%	80	15
Total behavioral control subscale ^b				
1st Tertile	27	12.3%	25	15
2nd Tertile	134	60.9%	50	10
3rd Tertile	59	26.8%	80	20
Total positive affect subscale ^b				
1st Tertile	32	14.5%	20	20
2nd Tertile	98	44.5%	50	20
3rd Tertile	90	40.9%	80	10
Total mental health index score ^b				
1st Tertile	31	14.1%	23.33	11.11
2nd Tertile	143	65%	47.78	12.22
3rd Tertile	46	20.9%	78.89	14.44

^a In depression lower score is worse.
^b The score is out of 100.
^c Some values are missing.

100. Table 5 compares the proportion and median score of mental health impairment stratified by gender. Data revealed significant difference in median total scores in each subscale and in the total MHI score as well. According to the MHI that lower score is worse, the first tertile is an estimate for the prevalence of mental health impairment. When comparing the prevalence of MHI in males (5%) to females (17.6%), it showed a significant difference (PV = 0.017). Table 6 shows tests between some demographic factors and each of PD and MHI scores. Results revealed no significant differences between median score of either PD or MHI with family history, age, income, occupation, and education level. There is a significant difference between median PD scores by nationality (PV = 0.02). On the other hand, there is no significant difference between medians of MHI scores by nationality

Table 4
Prevalence of cognitive impairment among MS patients stratified by gender in Kuwait (N = 224).

Cognitive impairment subscales ^a	Males				Females				PV
	n ^f	%	Median	IQR	n ^f	%	Median	IQR	
Attention/concentration^b									
1st Tertile ^d	29	47.5	5	6	61	37.9	4	6	0.191
2nd Tertile ^d	17	27.9	12	5	61	37.9	13	5	0.163
3rd Tertile^d	15	24.6	21	3	39	24.2	20	2	0.955
Total ^e	61	100	9	13	161	100	11	12	0.418
Retrospective memory^b									
1st Tertile ^d	29	47.5	2	5	71	44.1	4	5	0.645
2nd Tertile ^d	16	26.2	12.5	4	47	29.2	13	6	0.662
3rd Tertile^d	16	26.2	19.5	4	43	26.7	20	2	0.943
Total ^e	61	100	9	16	161	100	10	13	0.321
Prospective memory^b									
1st Tertile ^d	34	55.7	3.5	5	76	47.2	4	4	0.256
2nd Tertile ^d	19	31.1	13	3	45	28	13	4	0.639
3rd Tertile^d	8	13.1	21.5	3	40	24.8	20	1	0.058
Total ^e	61	100	7	11	161	100	9	14	0.094
Planning/organization^b									
1st Tertile ^d	34	55.7	2	5	79	49.1	4	5	0.375
2nd Tertile ^d	17	27.9	12	6	44	27.3	12	5	0.936
3rd Tertile^d	10	16.4	21	4	38	23.6	21	2	0.520
Total ^e	61	100	7	13	161	100	10	13	0.112
Total perceived deficits^c									
1st Tertile ^d	33	54.1	15	20	70	43.5	17	16	0.157
2nd Tertile ^d	16	26.2	49.5	13	52	32.3	51	18	0.381
3rd Tertile^d	12	19.7	81.5	15	39	24.2	81	10	0.472
Total ^e	61	100	31	46	161	100	37	46	0.176

^a In cognition higher score is worse.

^b Scores are out of 25.

^c Scores are out of 100.

^d The *p*-value was calculated using the two-proportion *Z*-test.

^e The *p*-value was calculated using Mann-Whitney *U* test.

^f Some values are missing.

(PV = 0.19). For MHI, there is significant differences in median scores by gender (PV = 0.001) but not with cognition impairment (PV = 0.176). Comparing MHI and cognition scores by nationality, results indicated that non-Kuwaiti Arabs scored worse when compared to Kuwaiti. However, there is a wider difference between Kuwaiti and non-Kuwaiti Arabs in the total cognition score. The effect of income on patients' mental health and cognition scores showed patients with monthly income less than 500 KD scored the worse in both PD and MHI. As income increased, there was an improvement in the scores. For patients with salaries over 500 KD, there was a linear increase in MHI score. As for cognition, all subgroups with salaries over 500 KD scored better compared to those with income less than 500 KD. Additionally, there were no differences between the wealthier subgroups (> 501 KD) themselves.

4. Discussion

The prevalence of cognition impairment among MS patients in Kuwait is about 23.3%, whereas, the prevalence for mental health impairment is about 14.1%. The prevalence of depression among MS patients in Kuwait is about 41.8%, while the prevalence of anxiety is 40.0% which are high compared to estimates in the literature (ranging between 19% and 54%) (Marrie et al., 2009; Raskind, 2008; Schiffer, 2005). The prevalence of MHI, including depression, was higher among females (females = 17.6%, males = 5%). When stratified by gender, the prevalence of cognitive impairment among males was 19.7% while it was 24.2% among females. A study in Italy found no significant difference in depression between genders (Mattioli et al., 2011). This disparity may be due to several reasons, e.g. the scoring procedure or instrument are different, and culture and population were different,

besides there was no age adjustment in this study. The current study revealed that the prevalence of cognitive impairment is 23.3%. In other studies, this number is anywhere between 40 and 65% (Bobholz and Rao, 2003; McIntosh-Michaelis et al., 1991; Rao et al., 1991). This could be due to higher education levels in Kuwait as education in public schools and universities is free of charge in Kuwait, the use of tertiles to describe the extent of impairment, and different scoring schemes. Similar to our study, other studies found multiple areas of cognition are affected, including attention, planning, and memory (Mattioli et al., 2011).

MS patients with income less than 500 KD had a median cognition score worse than all other income categories. This is possibly due to the fact that lower income patients have lower educational level. When comparing MHI and cognition scores by nationality, results indicated that non-Kuwaiti Arabs scored worse when compared to Kuwaiti. This could be due to the fact that the non-Kuwaiti Arabs have low income and less educated (labor force). Compared with the western world, the MS disease in Kuwait seems to have an earlier age at onset; it is thought to have relatively milder clinical severity, due to an effective national social-welfare system which makes modern treatments freely available to Kuwaiti nationals only, in addition to family social support.

5. Conclusions

The prevalence of cognition impairment among MS patients in Kuwait is about 23.3%, whereas, the prevalence for mental health impairment is about 14.1%. This study revealed that females have higher prevalence of mental health impairment compared to males. Moreover, Non-Kuwaiti Arabs have higher prevalence of cognition impairment compared to Kuwaitis. The data showed that 24.6% of the MS cases had a family history of neurological diseases. Additionally, MS patients with income less than 500 KD had a median cognition score worse than all other income categories. To the best of our knowledge, this is the first study in Kuwait to estimate prevalence of cognition and mental health impairment among MS patients. This study will provide health-care providers a sense of where to focus and put essential resources when designing an intervention to tackle this disease and so health care providers have a good starting point. Future interventions should be directed toward females, low income people, and non-Kuwaiti Arabs. Maybe allowing non-Kuwaiti Arabs and low income people access to free MS medications will substantially reduce cognition and mental health impairment among MS patients in Kuwait. Also, this is a cross sectional study and hence no causal relationships can be established. The study used a self-administered questionnaire thus potentially subject to some recall bias. The use of tertiles as cutoff points to estimate the prevalence might have produced a slightly liberal estimates. On the other hand, this study included a large sample size and used two validated questionnaires. It is to be noted that PDQ and MHI scales have low correlation with an objective neuropsychological testing procedure. Therefore, the estimated prevalence which is based on self-reported data and tertiles instead of an established cut-off point, should be interpreted with caution and shouldn't replace objective measures of physical and cognitive function tests including expanded disability status scale or magnetic resonance imaging.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 5
Prevalence of mental health impairment among MS patients stratified by gender in Kuwait (N = 224).

Mental health ^a impairment subscales	Males				Females				PV
	N ^d	%	Median	IQR	n ^d	%	Median	IQR	
Total anxiety									
1st Tertile	16	26.7	24	15	72	45.3	28	12	0.012
2nd Tertile	24	40	52	12	58	36.5	44	12	0.631
3rd Tertile	20	33.3	78	15	29	18.2	80	22	0.017
Total	60	100	52	40	159	100	36	28	0.004
Total depression									
1st Tertile	19	31.7	20	25	72	45.3	15	15	0.068
2nd Tertile	23	38.3	55	15	56	35.2	45	15	0.669
3rd Tertile	18	30	85	16	31	19.5	80	15	0.096
Total	60	100	52.5	50	159	100	35	45	0.010
Total behavioral control									
1st Tertile	3	5.0	25	.	23	15.1	25	19	0.053
2nd Tertile	37	61.7	50	13	96	60.4	50	15	0.862
3rd Tertile	20	33.3	80	18	39	24.5	85	20	0.190
Total	60	100	60	25	159	100	50	25	0.008
Total positive affect									
1st Tertile	5	8.3	10	15	27	17	20	15	0.106
2nd Tertile	27	45	50	20	71	44.7	50	15	0.963
3rd Tertile	28	46.7	80	14	61	38.4	80	5	0.264
Total	60	100	65	30	159	100	55	40	0.032
Total mental health index score									
1st Tertile^b	3	5.0	17.78	.	28	17.6	25.56	11.94	0.017
2nd Tertile	39	65	51.11	10	103	64.8	46.67	11.11	0.976
3rd Tertile	18	30	75.56	19.44	28	17.6	79.44	12.78	0.045
Total ^c	60	100	55	20.83	159	100	46.67	18.89	0.001

^a In depression lower score is worse. All scores are out of 100.
^b p-value was calculated using the two-proportion Z-test.
^c p-value was calculated using Mann-Whitney U test.
^d Some values are missing.

Table 6
Differences between median PD and median MHI scores by demographic factors for MS patients in Kuwait (N = 224).

Covariate	Total PD score		Total MHI score	
	Median	PV	Median	PV
Gender		0.176 ^a		0.001 ^a
Male	31		55	
Female	37		46.67	
Nationality		0.02 ^a		0.190 ^a
Kuwaiti	33.0		50	
Non-Kuwaiti Arabs	52.5		46.67	
Family history		0.827 ^a		0.197 ^a
Yes	36		51.67	
No	36		46.67	
Age		0.433 ^c		0.120 ^b
18–20	31		44.44	
21–30	36		47.78	
31–40	45		50.00	
41–50	38.5		50.56	
51–60	26		58.89	
Income		0.309 ^c		0.111 ^c
< 500	46		46.11	
501–1000	34		48.89	
1001–1500	33		50	
> 1501	34.5		54.44	
Occupation		0.858 ^c		0.468 ^c
Student	37		45.56	
Employed	36		48.89	
Unemployed	35.5		51.11	
Education		0.303 ^c		0.187 ^c
Primary	39.5		44.44	
High school	43		51.11	
College-university	35		48.89	
Higher education	28		56.67	

^a Mann-Whitney U test.
^b One-Way ANOVA.
^c Kruskal-Wallis test.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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