ORIGINAL RESEARCH

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Effects of long-term low-level solvent exposure on cognitive function

Abstract

Purpose: The effects of long-term low-level exposures to solvents on cognitive function were investigated.

Methods: A total of 389 workers at a gun factory, those exposed to solvents (n=193) and those that were not exposed to solvents during work (n=196), were included. All the workers were given a questionnaire. Cognitive function was evaluated by Mini-mental Status Examination (MMSE) and psychological status was assessed by Hospital Anxiety and Depression (HAD) Scale.

Results: No differences were found in the MMSE and HAD scores between solvent-exposed workers and control workers ($p>0.05$). In the workers who had used a mask for a longer time, orientation scores were lower. Daytime sleepiness was related to lower recall scores. Left-handed workers had higher total HAD scores than right-handed workers.

Conclusions: Long-term low-level exposure to solvents did not affect cognitive function in the workers, according to their MMSE scores. Duration of solvent exposure was also not related to MMSE Scores. Short sleep duration and daytime sleepiness may negatively affect cognitive function.

Manuscript submitted 15th February, 2012

Manuscript accepted 6th July, 2012

Clin Invest Med 2012; 35 (4): E190-E205.

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A solvent can be defined as “a liquid that has the ability to dissolve, suspend or extract other materials, without chemical change to the material or solvent”. Organic solvents have a wide range of usages, and are found as components of paints, pharmaceuticals, degreasing agents, adhesives, printing inks, pesticides, cosmetics and household cleaners and thus, are virtually everywhere. Commonly used solvents include isopropanol, toluene and xylene, solvent mixtures such as white spirits (mineral spirits) and chlorinated solvents such as methylene chloride, trichloroethylene and perchloroethylene [1].

Organic solvents are commonly used as mixtures rather than individual solvents in industry [2, 3]. Exposure to organic solvents has been reported to increase the risks for acute and chronic health effects among workers [2, 4]. Organic solvents have a special affinity for lipid-rich tissue (e.g., brain tissue) [5]. In cases of organic solvent exposure, diagnosis of “toxic encephalopathy” relies mainly on history, psychiatric findings and cognitive changes [6]. An association between duration of exposure and outcome, especially for cognitive and behavioral measurements, is unclear [7], although most occupational health specialists maintain that a dose-response relationship is necessary for a definitive diagnosis of neurotoxic disease [8].

Acute health effects on the central nervous system due to the inhalation of organic solvents include headache, dizziness and light-headedness progressing to unconsciousness, seizures and death [9]. Eye, nose and throat irritation may also occur with exposure to solvent mixtures [10]. Chronic exposure to low doses of solvents does not adversely affect pulmonary function, whereas it is associated with an increase in the prevalence of asthma [2]. Solvents have been demonstrated to cause mucosal irritation of the eyes and upper airways, but studies of pulmonary impairment following exposure have been limited and inconsistent. Solvent-mediated respiratory toxicity is biologically plausible [11].

In the acute stage of solvent intoxication, no special clinical, neurophysiological (EEG, evoked potentials) or radiological signs (CT, MRI) have been found except if concomitant hypoxia was present, resulting in cerebral edema or infarction. A discrete cortical-subcortical atrophy on CT or MRI scanning has been reported in some cases [12, 13]. Slowing of EEG activity was frequently seen in the acute stage. Only in such cases persistent cognitive deficit remained afterwards [12, 14] and the presence of deficits in neuropsychological testing shortly after the intoxication predicted a bad prognosis [12, 15, 16]. Long-term exposure to low airborne exposure concentrations is likely to produce slight pre-narcotic or irritation symptoms such as headache, nausea, inappropriate laughing or angeriness, dizziness, imbalance and eye irritation [12, 17]. In addition, as

for acute intoxications, chronic exposure conditions may lead to cortical and subcortical atrophy on CT-scan and diffuse diminished blood flow on Single Photon Emission Tomography (SPECT) examination [12,18].

Severe neurotoxic effects resulting from occupational exposure to organic solvents have been identified in earlier studies. Neurobehavioral endpoints such as altered cognitive functioning, motor and sensory disturbances, as well as mood and personality changes, were linked to solvent exposure. Atrophic changes in the brain, axon swelling and alterations in neurotransmitters were regarded as important neurological alterations underlying these behavioral changes [19,20].

A neuropsychological assessment is helpful in identifying/characterizing cognitive difficulties and can assist in identifying those with “pseudo-dementia” due to depression. A neurological examination, together with nerve conduction tests, where peripheral neuropathy is suspected, and magnetic resonance imaging (MRI) of the brain, may be helpful in diagnosis. Brain imaging is useful, both for excluding other neurological conditions and for identifying cerebral atrophy [21] or white matter lesions [22]. Radiological changes have also been described in individuals with solvent neurotoxicity [1].

Chronic exposure to organic solvents causes encephalopathy [9, 23], which typically results in CNS depression and psychomotor or attention deficit [24]. Some findings also suggest residual CNS dysfunction, persisting years after the end of exposure, particularly with long-term exposure to organic solvents [25]. Neuropsychological changes associated with acute and chronic exposure to organic solvents have been well documented in cross-sectional and longitudinal studies on those still at work or under 60 years of age [23, 26, 27].

The Montreal Protocol of 1987 was a landmark in environmental regulation [28] and led to restriction or phasing out of the production of a number of ozone-depleting solvents. The protocol arose from concerns about the adverse impact of some solvents, including chlorofluorocarbons, on tropospheric ozone. Recently, 1-bromopropane, a solvent introduced to replace ozone depleting agents such as 1,1,1-trichloroethane (methyl chloroform), has been shown to be neurotoxic in humans [29, 30].

Dose-response assessment is a critical part of the quantitative characterization of a chemical's potential to produce neurotoxicity [31]. Human studies covering a range of exposures are rarely available; therefore, animal data are typically used for estimating exposure levels likely to produce adverse effects in humans. Although dose-response functions in neurotoxicology are generally linear or monotonic, curvilinear functions, espe-

cially U-shaped or inverted U-shaped curves, have been reported [32].

Gun factory workers are exposed to many solvents, including toluene, acetone, butanol, xylene, benzene and trichloroethylene, over the course of many years, and this prolonged exposure may affect the cognitive and psychological status of the workers. In this study, the effect of long-term low-level exposures to solvents on cognitive functions was investigated. Exposure duration was 1 to 36 years. The effects of solvent exposure on cognitive functions were assessed using the MMSE test and the effects of solvent exposure on psychological status was assessed using the HAD Scale.

Materials and Methods

The study was undertaken by the Departments of Public Health and Pulmonary Medicine at the Kirikkale University Medical School between January and April 2007.

Participants

Our study was conducted on the workers at a gun factory in Kirikkale, Turkey, where gun parts are produced from raw materials. These parts are cleaned with solvents, and the workers are thus exposed to toluene, acetone, butanol, xylene, benzene and trichloroethylene during their work shift (continually 8 h/day, 5 days a week).

The study was performed on a total of 389 male workers divided into two groups: workers exposed to solvents ($n=193$) (chronic exposure duration was 17.74 ± 7.79 years, and ranged to 1 to 36 years); and a control group, those that were not exposed to solvents during their work in service areas such as security, office and engineering departments ($n=196$). Workers such as welders, carpenters and lathe operators were excluded from this study because they were not exposed to solvents but were exposed to other potentially harmful agents such as ammonia, cyanides, formaldehyde, nitrogen dioxide, isocyanates, ozone, phosgene, sulfur dioxide, phthalic anhydride, cadmium, chromium, nickel, beryllium and wood shavings (33).

Workers exposed to solvents and control workers were included in the study after signing an informed consent. In both groups, there were no history of stroke, traumatic brain injury or other pre-existing neurological or psychiatric conditions, and no history of usage of psychoactive medications.

Instrumentations

Questionnaire

A detailed occupational history was recorded for all the workers. The workers answered questions on their demographic characteristics, previous medical history including respiratory symptoms, sleep hygiene, sleep durations and daytime sleepiness. The questions related to solvent exposure, including daily, weekly, and total exposure duration (i.e., years of solvent usage), their habits of protective mask usage (present or absent, how often), and on their smoking (smoker, non-smoker, frequency) and alcohol use.

Mini-mental Status Examination (MMSE)

The MMSE (34-36) was administered to assess cognitive function. This test explores temporal and spatial orientation, short-term memory, computation, secondary memory, verbal attainment, and constructive ability. The main characteristics assessed were orientation (OR) (a total of 10 points), registration memory (RM) (a total of 3 points), attention and counting (AC) (a total of 5 points), recall (R) (a total of 3 points) and language (L) (a total of 9 points). Healthy subjects have scores > 23 (See Appendix 1) (34-36).

Hospital Anxiety and Depression Scale (HAD Scale) (37-39)

The HAD Scale was used to assess psychological status. The participants were asked to fill out the self-reported Hospital Anxiety and Depression (HAD) scale questionnaire for the assessment of psychological distress. The scale consisted of 14 questions in which the overall severity of anxiety and depression was rated on a 4-point Likert-type scale (0 to 3). Seven questions were related to anxiety and seven to depression (See Appendix 2) (37). Psychological distress score was defined as the total HAD score. The reliability and validity of the scale were evaluated by Aydemir and Guvenir in 1987 (38). The cut off point was 10 for the anxiety subscale and 7 for the depression subscale (39).

Methods

The workers exposed to solvents and workers in the control group were each given a questionnaire. MMSE and HAD Scale were used for all of the workers.

All the steps of the study were planned and carried out according to the principles outlined in the Declaration of Helsinki (40). Some components of the data on MMSE scores

were previously presented at the Meska 2007 Occupational Health and Safety Symposium, 281, Istanbul, 2007 (41).

Statistical Analysis

Statistical analyses were performed using SPSS (Version 16.0). For both groups, the difference between total MMSE scores, subgroups of MMSE (orientation, registration memory, attention and counting, recall, language); and total HAD scores were analyzed by ANOVA.

In the solvent-exposed group, the correlation matrix was made by Pearson correlation test between the factors affecting the total MMSE scores, subgroups of MMSE and total HAD Scores. The factors affecting the total MMSE scores, subgroups of MMSE and total HAD scores were analyzed by linear regression analysis; and the confounding factors having the greatest predictive ability for affecting total MMSE score, subgroups of MMSE and total HAD score were analyzed by linear regression analysis (backward linear regression). p value < 0.05 was considered statistically significant.

Results

Personal and occupational characteristics of the solvent-exposed workers and control workers are presented in Table 1. Education duration (years) of the workers in solvent-exposed group was 10.88 ± 1.38 years (range 1 to 18 years); and in control group, it was 10.67 ± 1.38 years (ranged from 5 to 16 years). The difference between educational years of the two groups was analyzed by ANOVA. The difference was not significant ($p=0.303$) [See on Table 1].

The difference between the ages of the groups was analyzed by ANOVA. The mean age of the solvent-exposed group (42.49 ± 6.48 years) was significantly higher than that of the control group (40.40 ± 8.41 years) ($p=0.006$). The mean solvent exposure time was 11.58 ± 8.29 years.

There was no significant differences in alcohol consumption or sleep duration between the two groups [Table 2]. Day-time sleepiness was higher in solvent-exposed group (analyzed by Chi-Square test, this difference was statistically significant, $p=0.007$, $X^2=7.234$). There was no significant difference between mask usage duration of the solvent-exposed group (5.22 ± 7.66 years) and control (unexposed) group (3.13 ± 6.82

TABLE 1. Personal and occupational characteristics of the workers in the study and control groups

Personal characteristics	Groups				P
	Solvent-Exposed (n=193)		Control (n=196)		
	Mean	SD	Mean	SD	
Age	42.49	6.48	40.40	8.41	0.006*
Alcohol consumption	n	%	n	%	p=0.259** $\chi^2=1.274$
No-usage	174	90.2	169	86.7	
<2 drinks per week	14	7.3	18	9.2	
2-5 per week	4	2.1	6	3.1	
>5 per week	1	0.5	2	1.0	
Occupational knowledge	Mean	SD	Mean	SD	
Work duration (year)	17.74	7.794	16.73	9.19	0.243*
Working days per week	5.04	0.21	5.11	1.16	0.409*
Working hours/day	8.15	0.52	7.99	0.55	0.005*
Mask usage (year)	5.22	7.66	3.13	6.82	0.555*
Education levels					
Education levels (years)	10.88	1.66	10.97	1.38	p=0.303

*ANOVA

*Chi-Square

SD, standard deviation

TABLE 2. Total MMSE scores and scores of subtitles; total HAD scores and sleep durations

MMSE Scores	Groups				p*
	Solvent-Exposed (n=193)		Control (n=196)		
	Mean	SD	Mean	SD	
Total MMSE score	28.88	1.573	28.73	1.621	0.368
Scores of subtitles					
Orientation	9.95	0.64	10.00	0.00	0.315
Registration memory	2.99	0.14	2.97	0.21	0.413
Attention and counting	4.16	1.18	4.05	1.30	0.367
Recall	2.78	0.53	2.77	0.51	0.823
Language	8.91	0.38	8.95	0.28	0.220
Total HAD score	12.69	5.49	13.16	6.17	0.434
Sleep duration	7.27	1.06	7.23	1.02	0.661

*ANOVA

SD, standard deviation

years) (ANOVA, $p=0.555$). As a protective measure, and according to current Turkish law, all workers (including controls) were requested to use their mask in their working places.

Total MMSE scores in the control group ranged from 23 to 30, and these values were within the normal range. For solvent-exposed workers, the total MMSE scores ranged from 21 to 30. Two workers had scores below the normal range (with scores of 21 and 22). There were no significant differences in total MMSE scores, subgroups of MMSE (orientation, registration memory, attention and counting, recall, language); and total HAD scores between the two groups [Table 2].

In the solvent-exposed group, a correlation matrix was made by Pearson correlation test between the factors affecting the total MMSE score, subgroups of MMSE and total HAD score [Table 3]:

1. There were positive correlations between "attention and counting"; and "recall"; and "total MMSE score".
2. In workers with longer sleep duration, "attention and counting" ability was also better.
3. In worker with daytime sleepiness, language values were poorer; and total HAD scores were higher.

4. In left-active-handed workers, total HAD scores were higher than for right-handed workers [Table 3].

5. There was significant positive correlation between solvent exposure (years) and mask usage (years) ($p=0.017$, $r=0.182$); and work duration (years) ($p=0.038$, $r=0.158$).

6. There was a significant correlation between mask usage (years) and orientation scores. In workers who used masks for longer, orientation scores were lower ($p=0.014$, $r=-0.188$) relative to workers (both exposed and unexposed to solvents) who wore their masks for fewer years [Table 3].

7. There were no significant correlations among duration of solvent exposure (years) and MMSE scores and total HAD scores [Table 3].

In the solvent-exposed group, the factors affecting the total MMSE score, subgroups of MMSE and total HAD score were analyzed by linear regression analysis (Table 4).

Dependent variables: Each of the MMSE scores (orientation; attention and counting; recall; language; and total MMSE score); and total HAD score.

TABLE 3. In the solvent -exposed group, correlation matrix by Pearson correlation test*

		Orientation	Registration memory	Attention and counting	Recall	Language	Total MMSE Score	Total HAD Score	Age	Solvent-exposure	Work duration (year)	Working days per week	Work-hours/day	Mask usage (Yes or no)	Mask usage (years)	Smoking	Cigarette-pack year	Use of alcohol	Sleep duration	Daytime Sleepiness	Active Hand
Orientation	r		-0.005	-0.051	-0.030	-0.018	-0.052	0.062	-0.084	-0.030	-0.058	0.016	0.021	0.040	-0.188	-0.042	0.030	0.022	-0.050	-0.070	0.017
	p		0.943	0.478	0.679	0.808	0.475	0.393	0.247	0.680	0.422	0.826	0.773	0.634	0.014	0.566	0.680	0.764	0.495	0.333	0.865
Registration memory	R	-0.005		0.071	-0.030	-0.018	0.132	0.036	0.073	0.040	0.118	0.016	0.021		0.052	-0.042	-0.011	0.022	-0.050	0.070	0.017
	p	0.943		0.326	0.679	0.808	0.067	0.624	0.317	0.581	0.101	0.826	0.773		0.496	0.566	0.875	0.764	0.495	0.333	0.865
Attention and counting	r	-0.051	0.071		0.352	0.114	0.852	-0.067	0.007	-0.034	0.099	-0.030	0.092	0.072	-0.025	-0.013	0.034	0.030	0.202	0.021	0.055
	p	0.478	0.326		0.000	0.116	0.000	0.354	0.927	0.639	0.171	0.677	0.205	0.391	0.748	0.856	0.640	0.674	0.005	0.768	0.576
Recall	r	-0.030	-0.030	0.352		0.277	0.565	-0.065	0.027	0.057	0.071	0.000	0.009	0.118	0.044	-0.038	0.066	-0.144	0.050	-0.066	0.059
	p	0.679	0.679	0.000		0.000	0.000	0.368	0.713	0.430	0.328	0.997	0.906	0.158	0.568	0.601	0.367	0.045	0.492	0.362	0.552
Language	r	-0.018	-0.018	0.114	0.277		0.438	0.014	-0.084	-0.058	-0.031	-0.010	0.005	0.041	0.109	0.110	0.143	0.010	0.012	-0.158	0.031
	p	0.808	0.808	0.116	0.000		0.000	0.849	0.247	0.421	0.671	0.887	0.941	0.626	0.156	0.127	0.048	0.886	0.874	0.029	0.755
Total MMSE Score	r	-0.052	0.132	0.852	0.565	0.438		-0.045	-0.027	-0.031	0.117	-0.029	0.067	0.097	0.039	0.016	0.070	0.124	0.122	-0.023	0.059
	p	0.475	0.067	0.000	0.000	0.000		0.537	0.714	0.667	0.106	0.684	0.352	0.245	0.614	0.830	0.332	0.087	0.092	0.756	0.551
Total HAD Score	r	0.062	0.036	-0.067	-0.065	0.014	-0.045		0.018	-0.161	-0.082	0.012	-0.111	-0.144	-0.174	0.095	0.127	0.056	-0.051	0.160	0.049
	p	0.393	0.624	0.354	0.368	0.849	0.537		0.804	0.026	0.258	0.867	0.126	0.083	0.023	0.187	0.079	0.439	0.486	0.026	0.617
Age	r	-0.084	0.073	0.007	0.027	-0.084	-0.027	0.018		0.347	0.600	0.036	0.000	0.000	0.046	-0.034	0.106	0.000	0.104	-0.023	-0.040
	p	0.247	0.317	0.927	0.713	0.247	0.714	0.804		0.000	0.000	0.617	0.763	1.000	0.550	0.640	0.146	0.992	0.153	0.753	0.686
Solvent-exposure (Years)	r	-0.030	0.040	-0.034	0.057	-0.058	-0.031	-0.161	0.347		0.474	0.097	0.093	-0.072	0.182	0.055	0.086	0.020	0.082	-0.010	-0.017
	p	0.680	0.581	0.639	0.430	0.421	0.667	0.026	0.000		0.000	0.177	0.201	0.389	0.017	0.450	0.235	0.785	0.262	0.893	0.864
Work duration (year)	r	-0.058	0.118	0.099	0.071	-0.031	0.117	-0.082	0.600	0.474		0.124	0.029	0.086	0.158	-0.093	0.063	0.070	0.042	-0.023	-0.149
	p	0.422	0.101	0.171	0.328	0.671	0.106	0.258	0.000	0.000		0.085	0.690	0.304	0.038	0.197	0.385	0.330	0.565	0.755	0.130
Working days per week	r	0.016	0.016	-0.030	0.000	-0.010	-0.029	0.012	0.036	0.097	0.124		-0.064	-0.050	-0.116	0.127	0.079	-0.009	-0.080	0.096	-0.001
	p	0.826	0.826	0.677	0.997	0.887	0.684	0.867	0.617	0.177	0.085		0.377	0.553	0.129	0.078	0.274	0.896	0.270	0.187	0.991
Work-hours/day	r	0.021	0.021	0.092	0.009	0.005	0.067	-0.111	0.022	0.093	0.029	-0.064		-0.063	-0.053	0.028	0.071	-0.018	0.004	-0.068	-0.015
	p	0.773	0.773	0.205	0.906	0.941	0.352	0.126	0.763	0.201	0.690	0.377		0.452	0.486	0.700	0.325	0.809	0.961	0.349	0.876
Mask usage (Yes or no)	r	0.040		0.072	0.118	0.041	0.097	-0.144	0.000	-0.072	0.086	-0.050	-0.063		0.403	-0.103	-0.092	-0.041	-0.165	-0.098	-0.082
	p	0.634		0.391	0.158	0.626	0.245	0.083	1.000	0.389	0.304	0.553	0.452		0.000	0.219	0.270	0.625	0.048	0.242	0.440
Mask usage (years)	r	-0.188	0.052	-0.025	0.044	0.109	0.039	-0.174	0.046	0.182	0.158	-0.116	-0.053	0.403		0.003	0.000	0.040	0.070	-0.101	0.000
	p	0.014	0.496	0.748	0.568	0.156	0.614	0.023	0.550	0.017	0.038	0.129	0.486	0.000		0.969	0.994	0.601	0.368	0.187	0.999
Smoking	r	-0.042	-0.042	-0.013	-0.038	0.110	0.016	0.095	-0.034	0.055	-0.093	0.127	0.028	-0.103	0.003		0.468	0.090	0.069	0.035	0.103
	p	0.566	0.566	0.856	0.601	0.127	0.830	0.187	0.640	0.450	0.197	0.078	0.700	0.219	0.969		0.000	0.215	0.344	0.630	0.294
Cigarette-pack year	r	0.030	-0.011	0.034	0.066	0.143	0.070	0.127	0.106	0.086	0.063	0.079	0.071	-0.092	0.000	0.468		0.158	0.064	-0.148	-0.005
	p	0.680	0.875	0.640	0.367	0.048	0.332	0.079	0.146	0.235	0.385	0.274	0.325	0.270	0.994	0.000		0.028	0.379	0.042	0.958
Use of alcohol	r	0.022	0.022	0.030	-0.144	0.010	0.124	0.056	0.000	0.020	0.070	-0.009	-0.018	-0.041	0.040	0.090	0.158		-0.032	-0.012	-0.056
	p	0.764	0.764	0.674	0.045	0.886	0.087	0.439	0.992	0.785	0.330	0.896	0.809	0.625	0.601	0.215	0.028		0.661	0.872	0.570
Sleep duration	r	-0.050	-0.050	0.20	0.050	0.012	0.122	-0.051	0.104	0.082	0.042	-0.080	0.004	-0.165	0.070	0.069	0.064	-0.032		0.075	-0.071
	p	0.495	0.495	0.005	0.492	0.874	0.092	0.486	0.153	0.262	0.565	0.270	0.961	0.048	0.368	0.344	0.379	0.661		0.302	0.478
Daytime Sleepiness	r	-0.070	0.070	0.021	-0.066	-0.158	-0.023	0.160	-0.023	-0.010	-0.023	0.096	-0.068	-0.098	-0.101	0.035	-0.148	-0.012	0.075		0.237
	p	0.333	0.333	0.768	0.362	0.029	0.756	0.026	0.753	0.893	0.755	0.187	0.349	0.242	0.187	0.630	0.042	0.872	0.302		0.016
Active hand	r	0.017	0.017	0.055	0.059	0.031	0.059	0.049	-0.040	-0.017	-0.149	-0.001	-0.015	-0.082	0.000	0.103	-0.005	-0.056	-0.071	0.237	
	p	0.865	0.865	0.576	0.552	0.755	0.551	0.617	0.686	0.864	0.130	0.991	0.876	0.440	0.999	0.294	0.958	0.570	0.478	0.016	

*r value shows correlation coefficient

TABLE 4. In the solvent-exposed group, linear regression analysis of affecting factors on total MMSE score, subtitles of MMSE and total HAD score

	MMSE Scores										Total HAD Score	
	Orientation		Attention and counting		Recall		Language		Total MMSE Score			
	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p
Age	-0.145	0.369	-0.015	0.932	0.212	0.207	-0.237	0.164	-0.069	0.691	-0.040	0.819
Solvent-exposure (years)	-0.013	0.925	-0.093	0.518	0.003	0.986	-0.149	0.298	-0.131	0.372	-0.159	0.257
Work duration (year)	0.023	0.895	0.156	0.388	-0.007	0.970	0.275	0.128	0.275	0.138	-0.016	0.931
Working days per week	0.012	0.920	0.115	0.375	0.006	0.964	-0.037	0.773	0.042	0.747	-0.056	0.656
Working hours/day	0.028	0.818	0.038	0.771	0.062	0.623	0.015	0.906	0.049	0.707	-0.164	0.185
Mask usage (yes or no)	0.248	0.076	0.204	0.166	0.244	0.093	0.019	0.897	0.214	0.154	-0.077	0.608
Mask usage (years)	-0.489	0.001	-0.109	0.443	-0.120	0.392	-0.007	0.959	-0.106	0.465	-0.086	0.579
Smoking	-0.084	0.565	-0.081	0.601	-0.156	0.306	0.139	0.366	0.039	0.803	0.024	0.875
Cigarette use (packs/year)	0.051	0.732	0.112	0.480	0.210	0.179	0.076	0.625	0.037	0.817	-0.002	0.988
Use of alcohol	0.065	0.608	-0.165	0.219	-0.194	0.142	0.051	0.698	0.105	0.440	0.128	0.373
Sleep duration (hours/day)	0.066	0.603	0.138	0.306	0.046	0.725	0.075	0.575	0.071	0.602	0.020	0.878
Daytime Sleepiness	-0.183	0.160	0.009	0.945	-0.039	0.770	-0.279	0.043	-0.076	0.587	0.171	0.216
Active hand	0.036	0.781	0.135	0.332	0.091	0.506	0.032	0.814	0.113	0.423	0.309	0.019
Total HAD Score	0.071	0.593	0.030	0.831	0.085	0.540	0.041	0.766	0.082	0.567		
MMSE Scores												
Orientation											0.637	0.527
Attention and counting											-0.440	0.661
Recall											0.435	0.666
Language											-0.081	0.936
Total MMSE Score											0.417	0.678

Independent variables: age; solvent-exposure (years); work duration (years); working days per week; working hours per day; mask usage (yes or no); mask usage (years); smoking; cigarette use (packs per year); use of alcohol; sleep duration; day time sleepiness; active hand; total HAD score; MMSE scores (orientation; attention and counting; recall; language; and total MMSE score).

In the solvent-exposed workers who used a mask for a longer time, orientation scores were lower (Beta: -0.489, $p=0.001$). In workers with daytime sleepiness, language values were lower ($p=0.043$, Beta=-0.279). In left-active-handed

workers, total HAD scores were higher than in right handed workers ($p=0.019$, Beta=0.309) [Table 4].

In the solvent-exposed group, the confounding factors having the greatest predictive ability for affecting total MMSE scores, subgroups of MMSE and total HAD scores were analyzed by linear regression analysis (backward linear regression) [Table 5]. Dependent and independent variables were as above.

In the workers who used a mask for a longer time, orientation scores were lower (Beta: -0.453, $p=0.000$). In the workers with higher daytime sleepiness, recall scores were poorer (Beta: -0.276, $p=0.018$). In left-handed workers, the total HAD

TABLE 5. Confounding factors with predictive ability for affecting mental scores

	Beta	p
MMSE Scores		
Orientation		
Mask usage (yes or no)	0.233	0.052
Mask usage (years)	-0.453	0.000
Recall		
Age (years)	0.213	0.070
Language		
Daytime sleepiness	-0.276	0.018
Total HAD Score		
Solvent-exposure (years)	-0.207	0.068
Active hand	0.368	0.002

In the solvent-exposed group, linear regression analysis (backward) of the confounding factors having the greatest predictive ability for affecting total MMSE score, subgroups of MMSE and total HAD score

scores were higher than in right-handed workers (Beta: 0.368, $p=0.002$) [Table 5].

Discussion

Organic solvents are encountered frequently in occupational settings [42, 43], and some are reported to produce clinical neuropsychological and neurological effects [43, 44]. Most solvents are volatile and can be readily inhaled by a worker. Some solvents, such as carbon disulfide, can, at high doses, produce specific neurotoxicological effects, including toxic polyneuropathy and a syndrome consisting of tremor and neuropsychological deficits in motor, affective, visuospatial, attention, executive and memory function [43-45]. Furthermore, repeated exposure to organic solvents is suspected of producing chronic encephalopathy [43, 46, 47]. Workers exposed to methyl-n-butyl ketone (an ink solvent and cleaning agent) displayed peripheral neuropathy involving sensory and motor changes of the hands and feet [42, 43]. Some solvents, including ethers, ketones, alcohols and various combinations, are commonly used in glues, cements and paints and can be neurotoxic when inhaled [43, 48, 49]. Repeated exposure to such solvents can lead to permanent neurological effects due to severe and permanent loss of nerve cells [43, 50]. Case-control studies have also shown that a history of organic solvent expo-

sure may be associated with increased risk of deficits similar to those seen with Alzheimer's disease [43, 51]. Exposure to solvents may be responsible for pseudo-dementia (depression) [52].

In the present study, workers at a gun factory were investigated for effects of long-term low-level exposures to solvents on cognitive functions. They were exposed to solvents such as toluene, acetone, butanol, xylene, benzene and trichloroethylene during their work shift (continually for 8 h/day, 5 days a week). Their occupational conditions, work duration and solvent-exposure time and protective mask usage were recorded. To evaluate the effects of solvent exposure on cognitive functions, MMSE test was applied and on psychological status, HAD scale was administered.

There were no differences between the total MMSE scores, subgroups of MMSE and the total HAD scores. Total MMSE scores between the two groups were not statistically different.

Statistical analysis showed no significant difference in the degree of cognitive impairment between the two groups; therefore, it was concluded that chronic solvent exposure was not related to cognitive impairment.

Previous studies have shown that exposure to manganese, solvents (methanol, toluene, carbon disulfide, and n-hexane) or carbon monoxide in an occupational setting may lead to central nervous system damage and Parkinsonism [53] and that, toluene and trichloroethylene were the solvents most likely to cause cognitive decline. In our study, the workers were exposed to toluene, acetone, butanol, xylene, benzene and trichloroethylene but no cognitive decline was seen. Hageman et al. [54] described three patients who had been exposed to various solvents for more than 20 years (25, 34, and 46 years). They presented with Parkinsonism, pyramidal signs, mild cognitive decline. Two patients had a predominantly axonal and sensory polyneuropathy of the lower legs with fasciculations in one of them. Hageman concluded that there is growing evidence that various organic solvents give rise to a Parkinsonism syndrome with pyramidal features in susceptible individuals. Lindström [55] also reported on cognitive and sensory and motor function in solvent-exposed workers. Solvents were trichloroethylene, toluene, styrene and mixtures of organic solvents. With most of these solvents, a decline in sensory and motor functions were found. Of the cognitive functions, short-term memory has proved to be especially sensitive to solvent exposure. Also, some decline in visuoconstructive abilities were found.

Cognitive decline occurs typically after the age of 65 years [55]. In our study, as the workers in the study (the mean age: 42.49 ± 6.48 years) and control groups (the mean age: $40.40 \pm$

8.41 years) were younger than 65 years, cognitive functions may not yet have been affected.

In solvent-exposed workers, correlation tests showed that, MMSE subtitles were related to each other, especially attention and counting, recall and total MMSE scores. Longer sleep duration was positively related with cognitive function. Daytime sleepiness had negative relation with language values. In left-handed workers and workers with daytime sleepiness, total HAD scores for solvent-exposed workers were higher than for control workers.

Surprisingly, workers who used a mask for a longer time had poorer orientation scores than the workers (both solvent-exposed and control workers) who wore the mask for shorter times.. Perhaps this was because workers who were exposed to higher levels of solvents tended to use the mask more frequently therefore, their cognitive functions may be evaluated as worse by MMSE.

In the workers with higher daytime sleepiness, recall scores, which evaluates immediate and short-term memory, were lower and it may be concluded that daytime sleepiness can lead to a lack of concentration and attention Daytime sleepiness may be a transient state that improves when the individual is well rested. Counting backwards is a better assessment of attention ability.

The European Consensus on Neuropsychological Characteristics, Assessment, and Guidelines for Diagnostics in 2012 [56] reported the neuropsychological impairment of chronic solvent-induced encephalopathy (CSE). The most common neuropsychological impairments in CSE patients are within the domains of attention, particularly the speed of information processing, memory, and motor performance. It appears that the influence of CSE on memory processes mainly involves immediate recall and generally involves verbal, visual and visuospatial material.

Workers with daytime sleepiness should be evaluated for Obstructive Sleep Apnea Syndrome (OSAS), and polysomnographic examination should be conducted [57,58]. In OSAS patients, during apnea periods, brain oxygenation is further decreased [57, 58]. The brain is sensitive to oxygen level in the blood and tissue [59, 60]. Although the brain represents only 2% of the body weight, the brain extracts approximately 50% of oxygen and 10% of glucose from the arterial blood [59]. Therefore, decreased oxygenation may also start reduction and destruction of cognitive functions. Thakur et al. [60] reported that among COPD patients, low baseline oxygen saturation was related to increased risk of cognitive impairment (OR for oxygen saturation $\leq 88\%$ (OR 5.45; 95% CI 1.014–29.2; $P =$

0.048). Conversely, regular use of supplemental oxygen therapy decreased the risk for cognitive impairment (OR 0.14; 95% CI 0.07–0.27; $P < 0.0001$).

In left-handed workers,, the total HAD scores were higher than for right-handed workers. In a large majority of the population, the right hand is active and nearly all machines and equipment are designed for right-hand use [61]. Thus, left-handed people, at least within our study population, may have or be predisposed anxiety and depression, though this is not supported by the literature [62], which leads to higher HAD Scores. In future studies, these issues should be investigated in detail.

The relationship of handedness and sleep position has been reported that that the majority of right handed people go to sleep on their right side, while left handed people go to sleep on their left side [63, 64]. Left-handed people think slightly faster than their right-handed counterparts. The differences were mild, but this does lend credence to mental discrepancies resulting being associated with handedness. Left-handed individuals might be more susceptible to learning handicaps, including child autism, stuttering and dyslexia. Other studies on the psychological effects of handedness have not concluded in any concrete results [65].

Berr et al. [66] investigated the impact of occupational exposure to solvents of TDI, trichloroethylene, perchloroethylene, dichloromethane, trichloroethane and benzene on cognitive ageing by the Digit Symbol Substitution Test (DSST) and the MMSE in 5242 participants (aged 55–65 years). These results suggest that occupational exposures to solvents may be associated later in life with cognitive impairment, even after taking into account the effects of education, employment grade, and numerous health factors [66]. Chronic low-level occupational exposure to organic solvents may have a negative impact on cognitive and psychological functioning [9, 23, 67].

In heavily exposed workers, solvents may have subtle effects on cognitive functions [68]. The cognitive domains affected by solvent exposures include attention, verbal memory, and visuospatial skills [69, 70]. There is some evidence that solvent neurotoxicity is commoner among those with at least 10 years of occupational exposure to solvents. Whether the important determinant of adverse effects is the lifetime (cumulative) exposure, the intensity of exposure, or peaks of exposure remains unclear.

Measurements of cerebral blood flow have documented decreased metabolism in both subcortical and cortical structures in workers occupationally exposed to solvents [71, 72]. In one solvent-exposed case, a positron emission tomographic scan reported decreased glucose uptake in the hippocampus

and amygdale [72]. Neurobehavioral studies have also speculated that medial temporal structures may be particularly vulnerable to the effects of organic solvents [73].

Taste, sight, and smell may be affected by exposure to solvents. Many, but by no means all, studies have found mild acquired colour vision losses in solvent-exposed workers [74]. Altered sense of smell has been described in solvent-exposed groups [75]. Anosmia may have an impact on safety where workers lose the ability to detect chemical releases. Animal studies using rats have found that some solvents are autotoxic [76], and co-exposures to noise and solvents lead to greater hearing loss than would be expected due to noise exposure alone [77]. In our study, sensorial loss was not detected in the solvent-exposed group.

Organic solvents are widely used in industry and are used in large quantities around the world. Chronic exposure to organic solvents induces central nervous system (CNS) damage. This damage may be clearly detected in older workers. In early working periods, MMSE may be used as a screening test for cognitive function of workers exposed to solvents. Cognitive impairment may be observed as an early sign and may be suspected with poorer total MMSE Scores [55].

In the present study, we did not find the cognitive impairment in our group of solvent-exposed workers. The reason for the different results in the literature and our study may be related to the type of solvent, concentrations of solvent, exposure features or age of workers. In addition, in solvent-exposed workers who used a mask for a longer time, orientation scores were poorer. It is reasonable to hypothesize that the workers who were more extensively exposed to solvents used masks more often.

We recommend that the workers should be reminded about possible harmful effects of solvent exposure. For prevention of solvent neurotoxicity, good occupational hygiene practice is the mainstay of managing solvent exposures: substitution with water based agents, engineering controls such as adequate local exhaust ventilation, administrative controls (for example, supervisors ensuring the storage of solvents in sealed containers when not in use), worker education, and finally the use of appropriate personal protective equipment that is fit for purpose [1]. In the future, studies should be planned with objectively defined solvent exposures.

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APPENDIX 1: Mini-mental State Examination (MMSE)³⁴⁻³⁶**Mini-mental State Examination****ORIENTATION (Total 10 points)**

Which year are we in.....()
 Which season are we in.....()
 Which month are we in.....()
 Which day of the month is today.....()
 Which day are we in.....()
 Which country are we living in.....()
 Which city are you currently in.....()
 Where is your district now.....()
 Which building are you currently located.....()
 Which flat are you located in this building.....()
 (Table, flag, clothes) (20 sec duration is allowed) Every correct answer is 1 point.....()

REGISTRATION MEMORY (Total 3 points)

Listen carefully to three names I will tell you soon and repeat after I finish.....()

ATTENTION AND COUNTING (Total 5 points)

Go back from 100 by removing 7. Continue until I say "stop"
 Each correct process is 1 point (100, 93, 86, 79, 72, 65).....()

RECALL (Total 3 points)

Do you remember the words you repeated above? Say the remembered ones
 (table, flag, clothes).....()

LANGUAGE (Total 9 points)

- a) What are the names of these objects you see (watch, pencil) (2 points) (Hold 20 seconds)
()
 b) Now, you listen carefully the sentence I will tell you; and after I finished, you repeat. "If and but, I do not want" (Hold 10 seconds) (1 point)()
 c) Now I will want you to do something: Please listen to me carefully and do what I tell you to. Take the paper on the table by your right/left hand, Using both hands, fold it in two; and put it on the ground." Total 3 points, time is 30 seconds, each of the correct procedure, 1 point()
 d) Now, I will give you a sentence. You read it and do what is told in the writing (1 point)
 CLOSE THE EYES (Do, on the back of the paper).....()
 e) Now, you write a meaningful sentence that comes into your mind on the paper I will give you (1 point)
()
 f) Draw the same figure I will show you (on the back of the paper) (1 point).....()

APPENDIX 2

This part is taken from Zigmond AS, Snaith RP (1983) 37.

The Hospital Anxiety and Depression Scale

NAME:

DATE:

FOLD HERE

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings, he will be able to help you more.

This questionnaire is designed to help your doctor to know how you feel. Ignore the numbers printed on the left of the questionnaire. Read each item and underline the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

A	I feel tense or 'wound up':
3	Most of the time
2	A lot of the time
1	From time to time, occasionally
0	Not at all

D	I still enjoy the things I used to enjoy:
0	Definitely as much
1	Not quite so much
2	Only a little
3	Hardly at all

A	I get a sort of frightened feeling as if something awful is about to happen:
3	Very definitely and quite badly
2	Yes, but not too badly
1	A little, but it doesn't worry me
0	Not at all

D	I can laugh and see the funny side of things:
0	As much as I always could
1	Not quite so much now
2	Definitely not so much now
3	Not at all

A	Worrying thoughts go through my mind:
3	A great deal of the time
2	A lot of the time
1	From time to time but not too often
0	Only occasionally

- D I feel cheerful:
- 3 Not at all
- 2 Not often
- 1 Sometimes
- 0 Most of the time
- A I can sit at ease and feel relaxed:
- 0 Definitely
- 1 Usually
- 2 Not often
- 3 Not at all
- D I feel as if I am slowed down:
- 3 Nearly all the time
- 2 Very often
- 1 Sometimes
- 0 Not at all
- A I get a sort of frightened feeling like 'butterflies' in the stomach:
- 0 Not at all
- 1 Occasionally
- 2 Quite often
- 3 Very often
- D I have lost interest in my appearance:
- 3 Definitely
- 2 I don't take so much care as I should
- 1 I may not take quite as much care
- 0 I take just as much care as ever
- A I feel restless as if I have to be on the move:
- 3 Very much indeed
- 2 Quite a lot
- 1 Not very much
- 0 Not at all
- D I look forward with enjoyment to things:
- 0 As much as ever I did
- 1 Rather less than I used to
- 2 Definitely less than I used to
- 3 Hardly at all

- A I get sudden feelings of panic:
3 Very often indeed
2 Quite often
1 Not very often
0 Not at all

- D I can enjoy a good book or radio or TV program:
0 Often
1 Sometimes
2 Not often
3 Very seldom

Now check that you have answered all the questions

FOR HOSPITAL USE ONLY

D (8-10) -----

A (8-10) -----