Assessment of cognitive deficits in obstructive sleep apnea with paper-based tests and choice reaction time in Indian population

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Obstructive sleep apnea (OSA) is a disease characterized by intermittent hypoxemia and sleep fragmentation. Studies conducted previously to assess cognitive functions in OSA have shown variable results. OSA is one of the increasingly common disorders in India. OSA typically shows 'tip of iceberg' phenomenon, i.e. very few diagnosed cases even with high prevalence. Thus, in a country with one of the highest number of road traffic accidents and occupational accidents, it becomes even more important to assess all OSA patients for cognitive functions especially with choice reaction time which is a very good indicator of real life situations such as vehicular driving and demanding occupational task. Thus, we compared cognitive functions in 30 cases of OSA with 30 age, sex and education matched control using standardized paper based tests and choice reaction time. We found choice reaction time to be severely affected in OSA. Amongst various domains of cognition, attention and executive functions were significantly affected in OSA. Also, there was decline in psychomotor abilities and memory.

Keywords: Cognitive functions, cognition, executive functions, obstructive sleep apnea, occupational accidents.

OBSTRUCTIVE sleep apnea (OSA) is characterized by repetitive episodes of reduced calibre or complete closure of oropharynx during sleep. These episodes lead to intermittent hypoxemia (IH) (dip in blood oxygen concentration) and fragmentation of sleep, which can give rise to variable cognitive impairments in OSA[1,2]. Cognition is defined as all mental processes involved in acquisition, processing, storage and retrieval of information. Different cognitive functions include attention, learning, memory, executive functions, language and psychomotor abilities[3]. Studies conducted previously to assess cognitive functions in OSA have shown variable results. Attention and memory have been consistently shown to be affected in OSA. Studies have been differing about deficits in executive functions and psychomotor abilities. None of the studies has assessed these patients with choice reaction time, which is very good indicator of processing speed, attention, psychomotor abilities, response inhibition and stimulus categorization together, thus mimicking real-life situations such as vehicular driving and demanding occupational task[4–8].

OSA is a very common disorder among obese individuals. It is a part of continuum spectrum of disorders from snoring to Pickwickian syndrome, with obesity as one of the most important driving factors along the spectrum (Figure 1)[1].

Prevalence of OSA in India is 7.5%, which is on much higher side than the western population[9]. OSA typically shows 'tip of iceberg' phenomenon, i.e. very few diagnosed cases even with high prevalence[10]. Also, it has causal relationship with metabolic syndrome (cluster of risk factors for diabetes and heart disease, viz. increased blood pressure, high blood sugar level, increased waist circumference and deranged lipid levels) and upper body obesity[11,12]. Thus, OSA is an increasingly common disorder in India with very high prevalence rate, associated with significant morbidity and mortality[1,11,12]. Hence, it becomes very important to assess effect of OSA on various cognitive domains in the Indian population. The present study was conducted in the Department of Physiology, Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai during 2012–2014. The study was approved by the institutional ethics committee.

Thirty recently diagnosed cases of OSA in the age group of 18–59 years were selected as study group. Thirty healthy age, sex and education matched individuals in the age group of 18–59 years were selected as control group[3,13]. Polysomnographically (sleep study) diagnosed patients of OSA were taken as cases before starting their treatment. OSA was defined as an apnea hypopnea index (AHI) of ≥ 5 on polysomnography[1,2,14] and Epworth sleepiness scale (ESS) of more than 10 (refs 1, 2).

All cases and controls were selected according to the inclusion/exclusion criteria. Cases and controls were explained in detail about the procedure to be performed in their vernacular language to their satisfaction. Written informed consent was obtained.

Inclusion criteria for cases were as follows: (i) Apnea–hypopnea index > 5 (ref. 14); (ii) ESS > 10 (refs 1, 2).

Inclusion criteria in controls to rule out OSA were as follows: (i) ESS < 10 (ref. 15); (ii) Body mass index (BMI) < 30 kg/sq. m (ref. 8); (iii) Neck circumference < 40 cm (ref. 16); (iv) No history of snoring and tiredness[17,18]; (v) No history of partners observation of apnea, choking and gasping during sleep[13,17]; (vi) Systolic BP < 120 mm Hg, Diastolic BP < 80 mm Hg.

Proper history was collected from all participants and anthropometric measurements were done. For assessing cognition, various paper-based tests, standardized for the Indian population in their native language (Marathi, Hindi or English) were conducted. All tests were administered under the guidance of a psychologist in the psychiatry department. Choice reaction time was assessed using apparatus RTM-608 manufactured by Bio-Tech, India (Table 1).

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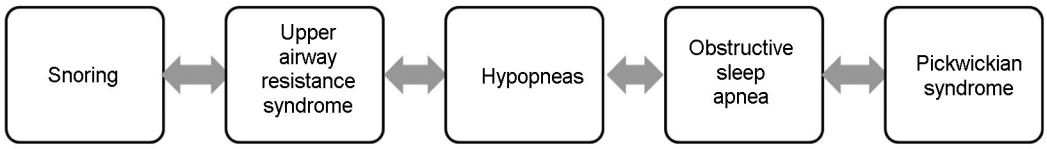

Figure 1. Spectrum of sleep disordered breathing[1].

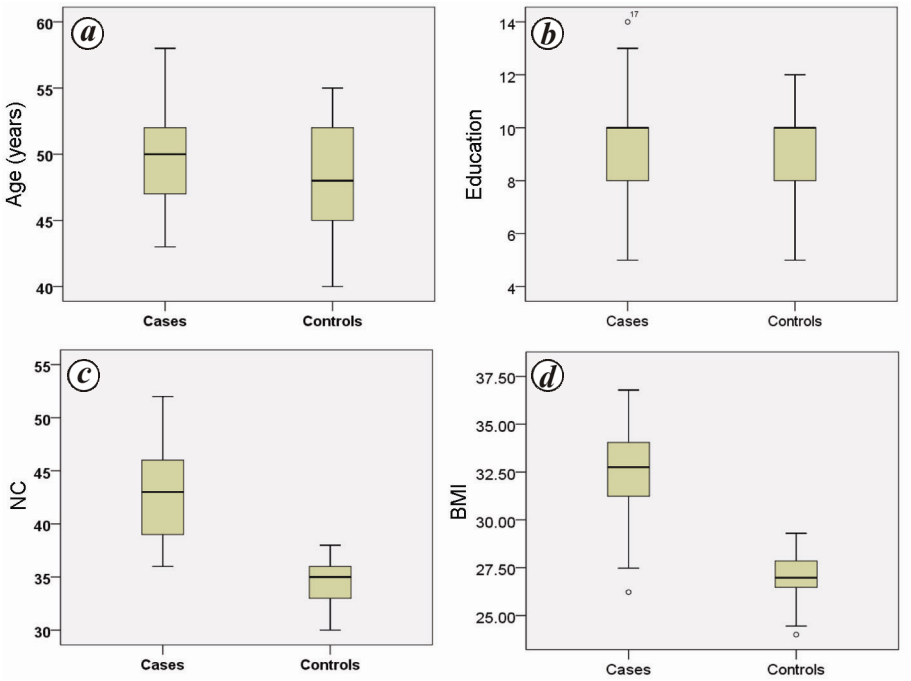

Figure 2. Comparison of mean values of demographic and anthropometric parameters between cases and controls. ***a***, No difference in mean age of cases and controls. ***b***, There was no difference in education level among cases and controls. ***c***, Neck circumference (NC) was significantly greater in OSA patients. ***d***, BMI was significantly greater in OSA patients.

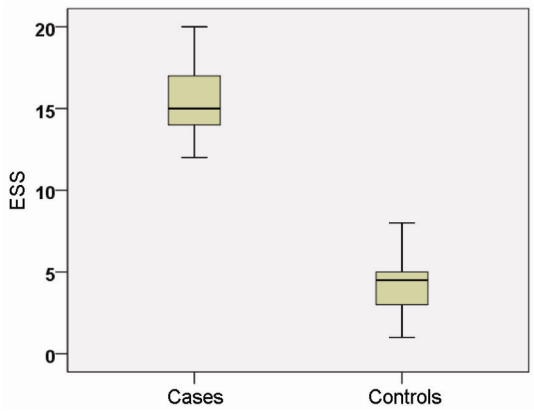

Figure 3. Comparison of mean values of Epworth sleepiness scale (ESS) between cases and controls, there was highly significant difference in ESS.

Statistical analysis was performed using unpaired *t*-test for all parameters. *P*-value < 0.05 was considered as statistically significant.

There was no statistically significant difference in age and education between cases and control. So both groups were comparable for cognitive functions. There was statistically significant difference in BMI and neck circumference (NC) of cases and control (Table 2; Figure 2). Also, there was statistically significant difference in ESS between cases and control (Table 3; Figure 3).

Comparison of mean values of various tests of cognition between cases and control is shown in Table 4 and Figure 4. All tests were selected to assess various domains of cognition.

We found both visual and auditory choice reaction time to be significantly decreased in OSA patients.

Concluding from the results of Stroop test, maze test, DST-B and phonemic verbal fluency, we found executive functions to be severely affected in all OSA participants. We assessed attention using digit symbol substitution (DSST), choice reaction time (CRT) and Stroop test and digit span test (DST). We found attention to be significantly affected in OSA participants. We assessed

Table 1. Tests of cognition

Test and cognitive domains assessed	Method	Scoring
Hindi mini-mental status examination (HMSE)[32]: General intellectual functions.	Participants were asked various questions given in HMSE.	Depending on response of participant, score was marked for a question. Total score ranged from 0 to 31 in HMSE.
Digit symbol substitution test (DSST)[3,33,34]: Psychomotor abilities, speed, attention, memory and visuomotor co-ordination.	Subject had to fill as many blank squares as possible in 120 sec with corresponding symbol given in key.	Total number of correct responses (DSST – Total corrects) and errors (DSST – Errors) committed were recorded.
Digit span test (DST)[3,33,34] (1) Digit span test-forward (DST-F): working memory, attention. (2) Digit span test backward (DST-B): working memory, executive function.	It consists of set of digits from two to nine digit sequences. Participants were asked to repeat each sequence exactly as told. DST-B is similar to digit forward except that participants were asked to repeat sequences in reverse order. It consists of sequences from three to six digits.	2 points were given when both sequences from set were repeated correctly and 1 point for repeating only one sequence. 0 point when both sequences were repeated incorrectly and test was stopped.
Logical short stories (LSS)[35]: Phonological loop of working memory, long-term verbal semantic memory.	Test material consists of two short stories which are divided into 21 smaller parts for scoring. Examiner read one story and asked subject to recall as many items from the story as possible immediately (LSS-I). And then, the second story was read. In delayed recall (LSS-D), participant was asked to recall each story after interval of 30 min.	1 point was given for each item correctly repeated. Points ranged from 0 to 21. Average of two stories was taken.
Maze test[3,33]: Planning and organization, behavioural inhibition, analysis and synthesis, organization and foresight, attention.	Participant was given printed maze with marked starting point in centre. He/she was asked to trace way out of maze without entering blind alley or crossing solid line or lifting pen. No back tracing was allowed.	Total time (maze time) taken by participant from once the maze was handed over to participant till tracing way out was measured. Total number of errors (maze errors) that included entering blind alley, crossing solid line and lifting of the pen during the trial were also noted.
Stroop test[34]: Behavioural inhibition, speed of processing information, attention, working memory, semantic activation and the ability to strengthen one's response characteristic.	Test material consists of names of colours written with ink different (incongruent) from written colour name. Victoria version of test contained total 24 items. This test consists of two parts. Participants were asked to perform both tasks as quickly as possible. a. In part I, participant read names of colour written ignoring ink colour in which they were written. b. In part II, subject told ink colour in which names of different colours were written ignoring verbal content.	Time taken to complete each task and number of errors (Stroop errors) were noted. Stroop interference was calculated by subtracting time taken in part II from part I.
Verbal fluency[3,34] (a) Semantic verbal fluency: Language, working memory, sematic memory. (b) Phonemic verbal fluency: Language, working memory, sematic memory and executive functions.	It has two parts. a. Semantic verbal fluency Here participant was asked to produce as many names as possible of a particular category in one minute. Animal and fruits were used as category. b. Phonemic verbal fluency Here subject was asked to produce as many words as possible beginning with specific letter in one minute. Letters used were F, A, S.	Total of all admissible words was taken as score.
Choice reaction time (CRT)[36,37]: Processing speed, attention, psychomotor abilities, response inhibition and stimulus categorization.	Reaction time apparatus RTM-608 manufactured by Bio-Tech, India was used. In case of Visual Choice Reaction Time (V-CRT), the examiner presented with any of the three visual stimuli (Red, Green or Yellow Lights) at random to the subject. The same procedure was repeated for auditory reaction time (A-CRT), where the buttons for High, Medium, Low frequencies were used by the examiner and the subject heard corresponding sound through headphone.	Three readings were taken for each visual and auditory choice reaction time test and the average of the three readings was taken as final result.

Table 2. Comparison of mean values of demographic and anthropometric parameters between cases and controls

Variable	Cases (mean ± SD)	Controls (mean ± SD)	Unpaired *t*-test (*P* value)
Age (years)	49.53 ± 3.95	48.27 ± 4.47	0.250 (not significant)
Education (years)	9.50 ± 2.28	9.40 ± 2.23	0.865 (not significant)
BMI (kg/m^2)	32.48 ± 2.33	26.95 ± 1.19	<0.001 (significant)
NC (cm)	42.60 ± 4.51	34.43 ± 1.96	<0.001 (significant)

Table 3. Comparison of mean values of ESS between cases and controls

Variable	Cases (mean ± SD)	Controls (mean ± SD)	Unpaired *t*-test (*P* value)
ESS	15.53 ± 2.08	4.53 ± 1.59	<0.001 (significant)

Table 4. Comparison of mean values of various tests of cognition between cases and controls

Variable	Cases (mean ± SD)	Controls (mean ± SD)	Unpaired *t*-test (*P* value)
HMSE	27.70 ± 1.49	28.20 ± 1.19	0.156 (not significant)
DSST – total corrects	27.20 ± 5.90	42.67 ± 9.22	<0.001 (significant)
DSST – percentage errors	4.83 ± 4.06	2.70 ± 2.39	0.017 (significant)
DST-F	7.33 ± 2.17	10.57 ± 2.10	<0.001 (significant)
DSS-B	3.10 ± 1.40	4.37 ± 1.50	0.001 (significant)
LSS-I	11.63 ± 1.59	13.33 ± 1.95	<0.001 (significant)
LSS-D	9.73 ± 1.76	11.10 ± 2.11	0.008 (significant)
Maze time (sec)	66.63 ± 14.54	56.30 ± 12.63	0.005 (significant)
Maze errors	2.27 ± 1.05	1.10 ± 0.80	<0.001 (significant)
Stroop interference	35.17 ± 8.42	24.77 ± 5.80	<0.001 (significant)
Stroop errors	1.73 ± 0.87	1.13 ± 0.90	0.011 (significant)
Sematic fluency	21.10 ± 2.47	25.70 ± 3.60	<0.001 (significant)
Phonemic fluency	27.50 ± 3.39	32.63 ± 4.00	<0.001 (significant)
V-CRT (ms)	0.674 ± 0.82	0.567 ± 0.41	<0.001 (significant)
A-CRT (ms)	0.652 ± 0.78	0.532 ± 0.40	<0.001 (significant)

participants for phonological loop of working memory and verbal semantic memory using LSS-I, LSS-D, DST and verbal fluency. We found phonological loop and verbal semantic memory to be impaired in OSA participants. DSST and CRT assessed participants for psychomotor abilities. We found psychomotor abilities and psychomotor speed to be impaired in OSA.

General intellectual functioning is commonly referred to as 'intelligence'. It refers to the measurement of general intellectual abilities (orientation, attention and concentration, sequence, visual-spatial abilities, verbal learning and memory, reading aloud, understanding and verbal repetition). We found no significant difference in general intellectual functioning of cases and control. This might be because tasks in Hindi mini-mental status examination (HMSE) such as vocabulary, information, object assembly, picture completion, visual tasks are more resistant to organicity (structural lesions).

Sharma *et al.*[13] found similar results in a study conducted on North Indian population. In that study, executive function was not found to be affected after adjusting for attentional and working memory deficits[13].

OSA is characterized by intermittent hypoxemia and increased inflammatory mediators. This leads to vasculopathy, oxidative stress, ion channel alterations and increased glutamate release which are further responsible for apoptosis and silent ischemic infarcts in prefrontal cortex and hippocampus[19–21]. Also, sleep fragmentation leads to decreased slow wave sleep, altered normal sleep related restorative functions and excessive daytime sleepiness[20,22]. All these ischemic, inflammatory and neuromodulatory changes at cellular and biochemical levels in brain are responsible for various cognitive deficits in OSA. The regions of brain which show greater vulnerability during hypoxemia are prefrontal cortex (executive functions) and hippocampus (memory). Imaging studies have consistently found diminished grey matter densities in these regions. Other regions which are frequently shown to be involved are parietal and temporal cortices, anterior cingulate cortex, thalamus, left entorhinal cortex, cerebellum and striatum[23–25]. All these organic or functional changes in brain are responsible for various cognitive deficits in OSA patients.

These cognitive deficits even though do not make these patients completely debilitated, do show their effect during demanding tasks of occupation, driving vehicle, etc. This is evident in the form of decreased work performance, occupational accidents and vehicular accidents seen in these patients[26].

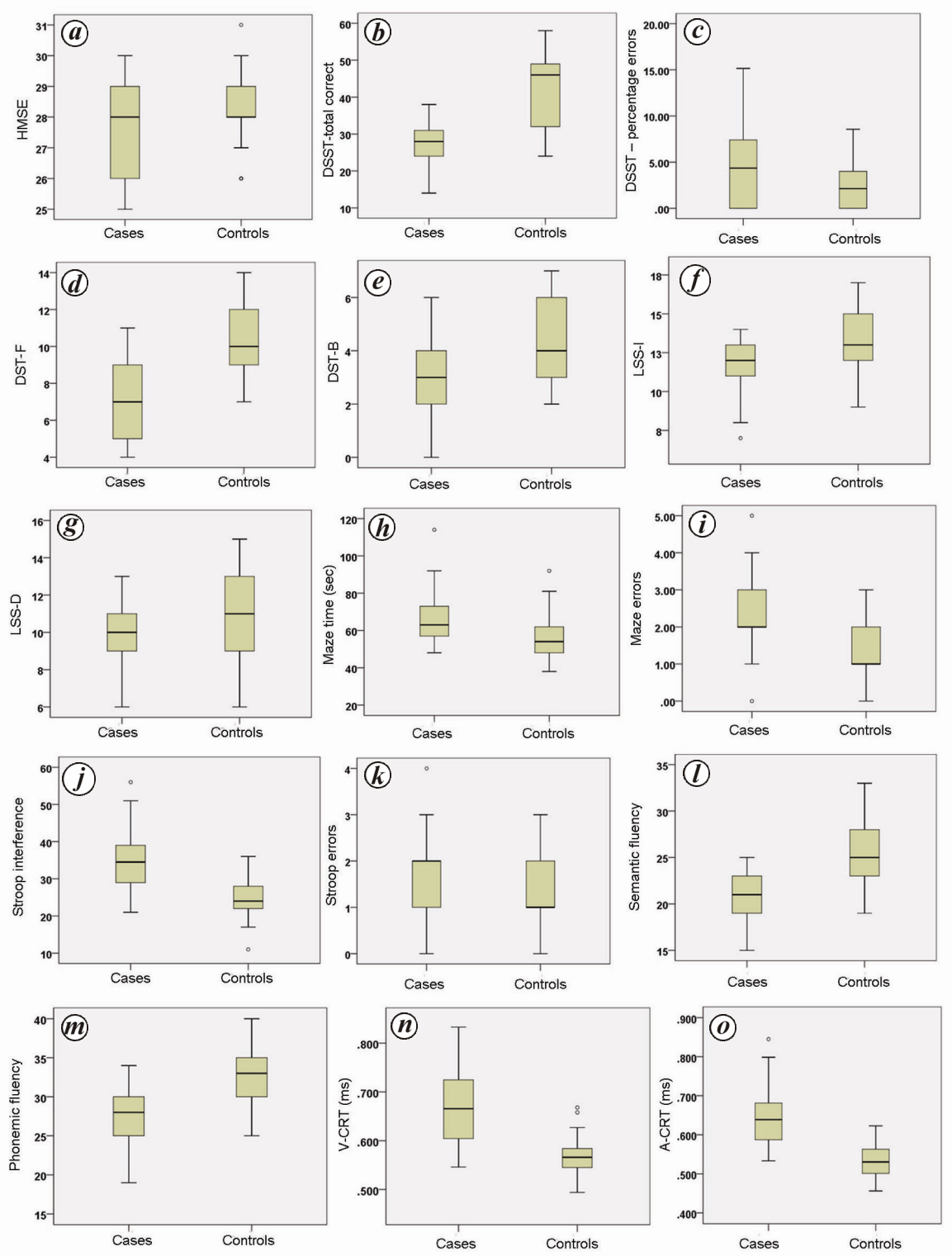

Figure 4. Comparison of mean values of various tests of cognition between cases and controls. ***a***, In HMSE, OSA patients performed as well as healthy participants. ***b***, OSA patients marked significantly lesser number of correct responses during DSST. ***c***, OSA patients committed significantly greater percentage errors during DSST. ***d***, OSA patients recollected significantly lesser number of digits during DST-F. ***e***, OSA patients recollected significantly lesser number of digits during DST-B. ***f***, OSA patients could not recollect as many items from stories as healthy participants. ***g***, In delayed recollection of stories, OSA patients recollected significantly lesser number of items. ***h***, OSA patients took significantly more time to solve mazes. ***i***, OSA patients committed significantly greater number of errors while solving mazes. ***j***, Stroop interference effect was significantly greater in OSA patients. ***k***, Number of Stroop errors committed were significantly greater in OSA patients. ***l***, Score of semantic fluency was significanly lower in OSA patients. ***m***, Score of phonemic fluency was significanly lower in OSA patients. ***n***, OSA patients were significantly slower during V-CRT and ***o***, OSA patients were significantly slower during A-CRT.

Asian Indian phenotype and metabolic syndrome associated with it, which is highly prevalent among Indians has causal relationship with OSA[27]. Further, OSA itself leads to increased sympathetic activity which is causative factor for some highly prevalent diseases such as hypertension, diabetes and myocardial infarction[2,11,12]. Thus, OSA and cognitive deficits caused by it might be much more prevalent than currently apparent. Thus, there exists tip of iceberg phenomenon, with very few diagnosed cases compared to prevalence of the disease. Additionally, this may be because of less awareness of OSA as a condition in a society where snoring is considered as a normal phenomenon and also may be due to lack of knowledge of OSA by healthcare worker[9].

With only 1% of total vehicles in the world, India accounts for as high as 6% of the world's road traffic accidents (RTA). The rate of RTA in India is 35 per 1000 vehicles which is one of the highest in the world and so is the fatality rate of RTA with 25.3 per 10,000 vehicles[28,29]. Thus, it is important to assess all patients of OSA for cognitive functions. All OSA patients should be assessed for cognitive dysfunction before issuing driving license and before assigning them to a job requiring high level of attention and executive function. So much was the impact of this disorder labelled as just acoustic nuisance (snoring) before 1970 that it was included in a Bill passed (Maggie's Law: National Drowsy Driving Act) in the United States 108th Congress on 27 February 2003 (ref. 30). Thus, making vehicular accidents by diagnosed OSA patients a criminal homicide and punishable offence[31]. Even though much is needed, no such law exists in India.

Overall, we found there was most significant difference amongst the scores of DSST, CRT, Stroop test and maze test in OSA patients and healthy subjects. These tests together consistently indicate severe deficits in executive functions and attention modality of cognition in OSA. These deficits limit performance during demanding tasks which is associated with decreased work performance, increased road traffic accidents and diminished quality of life. Thus, cognitive function tests should be routinely advised to the patients suffering from OSA. Accordingly, physicians should provide occupational advice to these patients. Also cognitive function test can become a relatively cheap study to assess prognosis and adherence of patients to continuous positive airway pressure (CPAP) which is a home-based treatment. Considering the risk posed by untreated and non-adherent patients to society in the form of occupational and motor vehicular accident along with high prevalence of OSA in India, legislations such as Maggie's Law should be considered in our country. It is recommended that OSA should be included in differential diagnosis of patient presenting with deficits in attention, executive function and psychomotor abilities of unknown etiology.

Limitations of the present study include attention and working memory deficits occurring in OSA, which can affect all tests of cognition used in this study. We have not assessed how deficits in attention and working memory affect tests assessing other cognitive domains such as executive function and memory.

Another limitation of the study is that all our patients were centrally obese and central obesity itself affects cognition which we have not ruled out. Further studies comparing OSA due to anatomical reasons, OSA with obesity and obese individuals without OSA are needed to confirm such findings.

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Emission inventory – a preliminary approach to primary pollutants

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Madurai is one of the most urbanized and emerging cities in India. Based on the conception of source-tracing and 'bottom-up' approach, the emission inventory was prepared using data from transport sector. The air pollutants such as CO, HC, CO_2, NO_x and particulate matter were considered and emissions estimated. The total emissions of CO, HC, CO_2, NO_x and particulate matter were found to be approximately 13.8 kilo tonne/year, 9 kilo tonne/year, 4.3 mega tonne/year, 12 kilo tonne/year and 1.02 kilo tonne/year respectively, during 2014. Three-wheelers and four-wheelers were found to be the major contributors towards emission of pollutants. This inventory study can be used to implement the mitigation strategies and also to support atmospheric modelling study.

Keywords: Air pollutants, emission inventory, emission factors, transport sector.

AMBIENT air quality is the most severe environmental concern in urban areas around the world, especially in developing countries. It has become the most essential topic for atmospheric research all over the world[1–5]. Over the past two decades in many emerging countries such as China and India, the increase of vehicular population has led to a great challenge in improving national oil security, urban air quality and public health[3,6–9]. The transport sector accounts for more than 50% of gross emission in urban as well as semi-urban areas from airborne pollutants[10] and vehicle emission controls have been implemented in different stages after the year 2000. India occupies the seventh largest position in vehicle producing countries[10]. This is a reason for urban air pollution in India[11,12]. Due to the usage of older vehicles with poor vehicle maintenance, insufficient road transportation and low fuel quality, the urban air pollution is endured in alarming levels[13–16].

Emission inventory is an inventory that reveals the amount of emission discharged into the atmosphere and a detailed emission inventory is required to understand the climate change issue from regional to global scales[17]. The emissions include some of the pollutants and greenhouse gases (GHGs) that are from all sources in a certain area within a specific time span and year. Transport sector is the major anthropogenic contributor of primary pollutants and GHGs like NO_x, SO_x, CO_2, CO, particulate matter (PM), etc.[18]. Several methods are available for the

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