International Psychogeriatrics (2014), 26:8, 1305–1316 © International Psychogeriatric Association 2014
doi:10.1017/S104161021400057X

Midlife metabolic syndrome and neurocognitive function in a mixed Asian sample

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ABSTRACT

Background: An association between metabolic syndrome (MetS) and disturbances in neurocognitive function has been identified in Caucasians but the nature and extent of impaired cognition in Asian MetS patients, who may be at greater risk of degenerative cognitive decline, remains unspecified.

Methods: A cross-sectional study was conducted at the National University Hospital of Singapore. Participants were recruited from a diabetes clinic at the National University Hospital. Fifty-three patients who met MetS criteria and 44 clinical controls were recruited. All participants were 55 years and above and community ambulant. Neurocognitive function was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB performances between MetS and control groups were examined with analysis of variance (ANOVA) and the relative contributions of vascular risk, and intrademographic factors on CANTAB scores were dilineated with stepwise regression analyses.

Results: Participants with MetS consistently performed significantly worse than controls across all CANTAB subtests. Education and Chinese race were found to be potential protective factors.

Conclusions: Executive and memory impairment is present in Asian patients with midlife MetS who may be particularly vulnerable to the detrimental impact of MetS in midlife.

Key words: metabolic syndrome, neuropsychological, CANTAB

Introduction

Cardiovascular risk appears to contribute to impaired cognition as people age. The metabolic syndrome (MetS) is a multifactorial disorder consisting of cardiovascular risk factors including hypertension, dyslipidemia, raised fasting glucose, large waist and obesity linked to heightened risk for Type 2 Diabetes Mellitus (T2DM), cardiovascular disease (CVD), and clinical stroke (Kwon *et al.*, 2006). MetS has been linked to several pathophysiological indices including impaired cerebrovascular reactivity (Giannopoulos *et al.*, 2010), increased carotid stiffness, intima-media thickness (Koivistoinen *et al.*, 2011), and carotid atherosclerosis (Romero *et al.*, 2009). Neuropathologically, MetS is associated with microvascular damage (Furie and Smith, 2007), leukoaraiosis (Panza *et al.*, 2011), silent brain infarction (Wang *et al.*, 2008), and increased brain atrophy (Muller *et al.*, 2011). Raz *et al.* (2007) showed that specific regions of the brain are more susceptible to vasculopathy including the hippocampus, entorhinal, and prefrontal cortex. Over five years, the fastest cortical degeneration was observed in the prefrontal cortex and the hippocampus. Significantly, fluid intelligence correlated with white matter hyperintensities (WMH) burden and declined with WMH progression whilst working memory declined with temporal lobe degeneration (Raz *et al.*, 2007). MetS has also been associated with general cognitive decline (Yaffe *et al.*, 2009) and amnestic mild cognitive impairment (a-MCI) (Feng *et al.*, 2013) although not always (Solfrizzi *et al.*, 2010). MetS has also been shown to predict vascular dementia (VaD; Solfrizzi *et al.*, 2010) and while there is some evidence supporting an association between MetS and Alzhiemer's dementia (AD; Vanhanen *et al.*, 2006), this association has not been consistent (Muller *et al.*, 2007; Solfrizzi *et al.*, 2010).

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https://doi.org/10.1017/S104161021400057X Published online by Cambridge University Press

Meta-analysis of MetS studies has revealed multiple-domain neurocognitive impairments but as yet no single replicable neuropsychological profile (Yates *et al.*, 2012). For example, Dik *et al.* (2007) found MetS was associated with slower speed of information processing, memory and fluid intelligence, a proxy variable of executive function. Hassenstab *et al.* (2010) showed that MetS was significantly related to deficits in episodic (short-term) memory, new learning and executive dysfunction. Segura *et al.* (2009) found that MetS was primarily associated with deficits of speed of processing, immediate memory and executive dysfunction akin to vascular cognitive impairment (VCI). In contrast, large-scale population studies by Muller *et al.* (2010) found MetS was associated with memory and visuospatial impairment but not executive dysfunction whereas Roberts *et al.* (2010) reported no association between MetS and either a-MCI or na-MCI.

Whilst research into MetS continues in western countries, a smaller number of studies have examined the syndrome in Asians. Several factors make the MetS syndrome of particular concern to Asia including (but not limited to) increased energy consumption with a concomitant reduction of physical activity (Janus, 2004); lower high-density lipoprotein (HDL) and higher levels of small, dense low-density lipoprotein (LDL) compared to Caucasians in some societies (Gama *et al.*, 2002); higher proportions of body fat but lower adiposity thresholds compared to Caucasians of the same age, gender, and body mass index (BMI; World Health Organization, 2004) that may be associated with greater risk for hypertension and hyperlipidemia in some societies; and traditionally high rates of ischaemic heart disease, cerebrovascular disease (Misra and Khurana, 2009).

MetS in Asia is likely to vary greatly from the west according to region, diet, and lifestyle, socioeconomic and cultural factors, and urbanization. In India, for example, estimates suggest that up to one-third of urban dwelling adults have MetS (Misra *et al.*, 2007). In Pakistan, the incidence increases to 49% when classified according to the International Diabetes Federation (IDF) definition and modified National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria (Basit and Shera, 2008). Singapore, a country which consists of a majority population of migrant Chinese, and minority indigenous Malay and migrant Indian populations, has varying rates of MetS. Using a modified NCEP ATP III definition in a health survey of 4,723 adult Singaporean participants, Tan *et al.* (2004) reported prevalence of 28.8% in Indians, 24.2% in Malays, and 14.8% in Chinese. A higher rate (26%) was reported by Ho *et al.* (2008) in a community sample of 1,352 Chinese Singaporean older adults without CVD, stroke, or cognitive impairment (Mini-Mental State Examination, MMSE <24). In many other Asian countries, the incidence of MetS is presently unknown.

The relationship between MetS and neurocognitive impairment in Asians is not well documented. In Singapore, Ho *et al.* (2008) found a negative association between MetS and overall cognitive decline predefined as at least 2-point drop in MMSE total score at follow-up one to two years after baseline assessment, but the association was limited to the Chinese population only. Ng (2009) reported mean MMSE scores amongst different clinical conditions including hypertension and diabetes but found no significant associations with decline. In South Korea, Lee *et al.* (2009) found no significant relationship between MetS and overall cognitive abilities using the Korean version of MMSE (K-MMSE). However, it is important to note that the MMSE is a limited tool for the assessment of neuropsychological status and is unlikely to tap the subtle aspects of cognitive change in the MetS population.

Feng *et al.* (2013), in predominantly Chinese Singaporean sample, was the first to demonstrate a direct positive association between MetS and a-MCI when a more comprehensive battery of neuropsychological tests was used including tests of memory, attention, executive function, language, and visuospatial skills. Of particular note, central obesity, the principal component of MetS, showed increased odds of association with a-MCI. Unfortunately, insufficient sample size precluded the authors from examining the relationship between MetS and na-MCI, and the association between MetS and impaired cognitive functioning that includes Malays and Indian ethnicities were not examined directly.

Aim of the study

Currently, MetS is not well understood in Asia, and past neuropsychological studies in Asian populations are limited. The present investigation aimed to examine the neurocognitive profile of MetS in Asians using sophisticated and subtle neuropsychological measures and to explore the influence of individual risk and/or protective factors (age, race, education level) and vascular risk factors on performance indices.

Methods

Participants

Participants in the present study were identified from an on-going cross-sectional correlational study

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conducted by the National University Health System (NUHS). Participants were Singapore citizens or Singapore permanent residents aged 55 years and above. The rationale for this age cut-off was that midlife risk factors may provide as a more accurate indication of the total sum of vascular risk in a lifetime (Debett and Seshadri, 2009).

Medical history was taken at the time of enrollment in order to exclude participants with known or suspected histories of neurological diseases, psychiatric illnesses, or other conditions which could affect neurocognitive performance. Exclusion criteria were: formal diagnosis of dementia or cognitive impairment, current cancer treatment (radiotherapy or chemotherapy), depression, visual or hearing impairment, wheelchair-bound and living in a nursing home. Participants were recruited primarily from the Diabetes Clinic at the National University Hospital (NUH) while controls included spouses, relatives, or friends of the participants in the experimental group.

In total, 97 participants were identified from study referrals who had their MetS status determined from medical records and history, blood tests, and physical examination. From this sample, 53 participants, who met criteria for MetS, were classified as the MetS group, and 44 participants, who demonstrated varying degrees of vascular risk (i.e. presence of at least one vascular risk factor) but did not meet criteria for MetS, were included as clinical controls. Importantly, the clinical control group demonstrated characteristics that closely reflected the midlife health status of the broader Singaporean population in that they possessed at least one vascular risk factor. The study was approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) and informed consent was obtained from all participants.

Measures

MetS at baseline was determined using modified IDF criteria (Alberti *et al.*, 2005) that included obesity. Obesity is considered to be a premature contributing factor that is becoming more widespread in Asia. Local evidence indicates that approximately half of adult Singaporeans with even relatively low levels of BMI have at least one cardiovascular risk factor (Deurenberg-Yap *et al.*, 2001). As such a revised BMI cut-off point of $\geq$23 kg/m^2 plus the presence of at least two of the following criteria was applied including: (1) elevated blood pressure: systolic $\geq$130 or diastolic $\geq$85 mm Hg, using anti-hypertensives or treatment for previously diagnosed hypertension; (2) elevated fasting plasma glucose: $\geq$5.6 mmol/L, using any anti-diabetic drugs or treatment of previously diagnosed T2DM; (3) elevated triglycerides $>$1.7 mmol/L or using any lipid-lowering drugs; (4) low HDL-cholesterol $<$1.03 mmol/L in men and $<$1.29 mmol/L in women, or using lipid-lowering agent.

For participants who were recruited from the NUH Diabetes Clinic, details of vascular conditions of interest (i.e. T2DM, hypertension, and hyperlipidemia) were obtained from medical records. These records were matched with self-reports. For participants whose medical records were unavailable, self-reports for physician diagnosis of diabetes, hypertension, cardiovascular heart diseases and stroke, or treatment for these conditions were verified by the research assistant during the interview session. Participants were asked to produce all current medications and treatments for diabetes, hypertension, high cholesterol, heart diseases, and stroke, and they were noted.

Neuropsychological assessments

Mini-mental state examination

General cognitive function was assessed using the MMSE (Appendix C), a 23-item test which incorporates short questions on orientation in time and place, attention, language, memory, and visual construction.

Cambridge neuropsychological test automated battery (CANTAB)

The associations between MetS and memory and executive functioning were examined using the Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB has been used extensively to assess multiple neuropsychological functions and neural substrates, and has been validated in elderly and clinical populations. The test battery was chosen for its reduced reliance on verbal skills that may confound performance on testing in some cultures, and its ability to identify subtle impairments in psychomotor processing speed, memory, and executive function. The non-verbal nature, standardized procedures, and stable psychometric properties as established in the West and in Taiwan (56) made the CANTAB ideal as a prospective screening tool for cognitive impairment and early dementia.

In this study, the tailored CANTAB comprised of four key tests:

Paired-associate learning (PAL)

PAL assesses visuospatial memory and associative learning. Participants were required to remember up to eight pattern–location associations. Initially, colored patterns were presented sequentially in

https://doi.org/10.1017/S104161021400057X Published online by Cambridge University Press

boxes on the monitor screen at different locations. The patterns then appeared sequentially in the center of the screen and participants were instructed to remember and later locate the box in which each pattern was initially presented. If participants were able to correctly match the patterns to the respective locations, the test proceeded to more difficult stages. If incorrect response was made, all the patterns would reappear in their original locations, followed by another recall phase. The test would be terminated after ten trials if all patterns were consistently matched incorrectly. Performance was scored based on PAL Trials in four levels of difficulty (two-shape, three-shape, six-shape, and eight-shape stages) which measured the total number of presentations required to correctly locate all the patterns in each stage.

Intra-extra dimensional set shift (IED)

IED assesses visual discrimination and attentional flexibility. Participants were required to learn a nine-stage string of two-alternative forced choice discriminations starting with a simple discrimination and its reversal of one dimension. Compound discrimination and its reversal were then assessed with the addition of another alternative dimension overlapping the shapes. Success was dependent on the ability to shift attention to a different pattern within a previously relevant perceptual dimension (intra-dimensional shift, IDS) and then shift attention to a different aspect of a previously unrewarded perceptual dimension (extra-dimensional shift, EDS). Participants proceeded through the tests by fulfilling a set of learning criteria at each stage (six consecutive correct responses). If unable to reach the criteria after 50 trials at any stage, the test was terminated. Attentional flexibility was scored based on the aggregate of IED Errors (blocks 6 and 8), which measured the number of errors taken to successfully complete an IDS and EDS respectively.

Stockings of cambridge (SOC)

SOC measures spatial planning and spatial working memory (SWM). Participants were required to plan and carry out a set of movements on the touch screen to replicate a particular arrangement of colored balls. At the start of each trial, three suspended vertical stockings and three colored balls were presented. In the problem solving condition, the objective was to move the colored balls, one move at a time, to replicate the target arrangement within a specified number of moves (i.e. three, four, five moves). Performance was scored based on two indices: (1) problems solved in minimum moves: recording the number of occasions upon which the participant successfully completed a test problem in the minimum possible number of moves; (2) mean moves (three-move, four-move, and five-move problem): the mean number of moves taken in excess of the specified minimum number, but within the maximum allowed.

Spatial working memory

SWM measures ability to retain spatial information and to manipulate remembered items in working memory; it also assesses strategy. Participants were instructed to search through a number of boxes presented on the screen to find blue tokens hidden inside. Each box only contained one token per trial. The aim of the task was to recall and to avoid those boxes in which a token had already been located. Participants were able to search the boxes in any particular sequence they wished. Performance was based on effective strategy across four to eight box arrays.

Procedure

At the time of study entry, each participant underwent an in-person interview of general health status and function, medical history, physical examinations, followed by the administration of neuropsychological test battery by trained research assistants. The interview was conducted in English or Mandarin, according to the participant's dominant language. Interview and neuropsychological test battery scripts were standardized. In the event where participants did not understand English or Mandarin, a family member fluent in English or Mandarin assisted in translation. Where possible, participants were tested in their own home. The assessment was administered in one session, usually lasting 2 h each.

Statistical analysis

Baseline demographic variables (age, gender, race, and education level) were compared using *t*-tests and χ^2. Analysis of variance (ANOVA) compared the CANTAB neuropsychological performance indices between the MetS and control groups. Repeated measures ANOVA examined the interaction between groups and the difficulty levels of tasks for performance indices with different levels of difficulty. Stepwise multiple regression analyses were performed to determine the influence of independent demographic characteristics and MetS components on outcome variables that were found significant in the prior ANOVA. All data were analyzed with SPSS, version 21.0 (IBM SPSS,

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Table 1. Comparisons of demographic characteristics and mean scores of MMSE among MetS and control group

	METS ($n = 53$) MEAN ± SD	CONTROL ($n = 44$) MEAN ± SD	TEST STATISTICS	*df*	*p*-VALUE
Age	65.62 ± 7.41	64.16 ± 7.01	0.99	95	ns
Gender – Male	29 (54.7)	26 (59.0)	0.19	1	ns
Gender – Female	24 (45.3)	18 (40.9)			
Education	10.42 ± 4.29	10.32 ± 3.39	0.12	95	ns
Race – Chinese	35 (66.0)	41 (93.2)	10.76	3	<0.05
Race – Malay	4 (7.5)	1 (2.3)			
Race – Indian	11 (31.4)	2 (4.5)			
Race – others	3 (5.6)	0 (0)			
BMI	26.86 ± 3.50	22.34 ± 2.90	6.83	95	<0.001
Hypertension	42 (79.2)	13 (29.5)	24.19	1	<0.001
Hyperlipidemia	48 (90.6)	14 (31.8)	35.98	1	<0.001
Overweight/obese	53 (100)	19 (43.2)	40.57	1	<0.001
Type 2 Diabetes Mellitus	48 (90.6)	8 (18.2)	51.62	1	<0.001
MMSE	27.43 ± 2.24	27.74 ± 1.85	− 0.73	94	ns

Note: Figures shown are *n* (%).
MMSE = Mini-Mental State Examination; BMI = body mass index.

Inc.) and an alpha level of 0.05 was used to assert statistical significance.

Results

Demographic variables

The final sample consisted of 97 participants; 56.7% ($n = 55$) were male, 78.4% ($n = 76$) were Chinese, 5.2% ($n = 5$) were Malay, 13.4% ($n = 13$) were Indian, and 3.1% ($n = 3$) were Mixed race. The average age of the study participants was 64.96 years (SD = 7.23) and mean education level was 10.37 (SD = 3.89).

Table 1 shows the demographic characteristics and mean MMSE scores between the MetS group and the control group. Participants in the MetS group ($n = 53$) had significantly greater BMI, prevalence of hypertension, elevated triglycerides, T2DM, and were significantly overweight or obese compared to the control group ($n = 44$). Within the control group, the prevalence of T2DM, hypertension, hyperlipidemia, and overweightness and obesity matched those within the general local elderly population. There were no significant differences between groups in age, education, and gender proportion. There was no difference in mean MMSE scores between the MetS and control groups. Significant differences in racial proportions were present between the two groups ($p = 0.013$), hence race was included as a covariate in all subsequent analyses.

Table 2 provides a summary of the ANOVA results of CANTAB performance for MetS and control groups.

Paired associates learning

The key variables of interest for PAL were total trials (two, three, six, eight shapes adjusted) and total errors (two, three, six, eight shapes adjusted). Two separate repeated measures analyses of variance were performed, with total trials and total errors as the within-participants factors and group as the between-participants factor. Mauchly's test indicated that the assumption of sphericity had been violated in both total trials and errors analyses (χ^2 (5) = 58.22, $p < 0.01$; χ^2 (5) = 232.25, $p < 0.001$), therefore degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity ($\varepsilon = 0.71$ and 0.49 respectively). A significant main effect was found for total trials (two, three, six, eight shapes), (F (2.13, 187.32) = 38.12, $p < 0.01$) indicating that, overall, as the difficulty level increased, the number of trials required to complete the test increased. There was no significant main effect for group (F (1, 88) = 0.40, $p = 0.528$). The interaction effect was within the range of significance (F (2.13, 187.32) = 2.66, $p = 0.069$; Winer, 1970) and permitted *post hoc* testing. *Post hoc* with Bonferroni correction for significance indicated that in the eight-shapecondition, the average number of total trials required was significantly higher in the MetS group ($M = 5.50$, SD = 2.89) than in the

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Table 2. CANTAB performance for MetS and control group

CANTAB OUTCOME MEASURE	*df*	*F*	*p*-VALUE
PAL			
Group	1, 88	0.40	ns
PAL total trials (2, 3, 6, 8 shapes adjusted)	2.13, 187.32	38.12	<0.01*
Group × MetS × PAL total trials (two, three, six, eight shapes adjusted)	2.13, 187.32	2.66	0.06
IED			
Group	1, 92	4.24	<0.05
IED Errors (blocks 6 and 8)	1, 92	4.95	<0.05
Group × MetS × IED Errors (blocks 6 and 8)	1, 92	0.43	ns
SOC			
SOC problems solved in minimum moves	1, 89	4.66	<0.05
Group	1, 89	5.09	<0.05
SOC mean moves (three, four, five moves)	1.71, 152.24	12.24	<0.01
Presence of MetS × SOC mean moves (three, four, five moves)	1.71, 152.24	1.93	ns
SWM			
SWM strategy (four to eight boxes)	1, 91	2.75	ns

*$p < 0.05$.
CANTAB = Cambridge Neuropsychological Test Automated Battery; PAL = paired-associate learning; IED = intra-extra dimensional set shift; SOC = stockings of Cambridge; SWM = spatial working memory.

control group ($M = 4.20$, SD = 2.83), $t(93) = 2.20$, $p = 0.030$ (Figure 1). For total errors, no significant main effects or interaction effects were present.

Intra-extra dimensional shift

A repeated measures ANOVA was performed with IED Errors (block 8) and IED Errors (block 6) as the within-participants factor, and group as the between-participants factor. A significant main effect was found between block 8 and block 6, (F (1, 92) = 4.95, $p = 0.029$), revealing that more errors were committed in the EDS (block 8) than the IDS (block 6). A significant main effect was also found for group (F (1, 92) = 4.24, $p = 0.042$), as the MetS group committed more errors in the block 8 and block 6 conditions combined than the control group. No significant interactions were present.

Stockings of Cambridge

ANOVA revealed significant group differences, (F (1, 89) = 4.66, $p = 0.034$) with the control group solving significantly more problems using an optimum strategy compared to the MetS group. Repeated measures ANOVA, with mean moves (three-, four-, five-move problems) as the within-participants factor and group as the between-participants factor was performed. Mauchly's test indicated that the assumption of sphericity had been violated (χ^2 (2) = 16.31, $p < 0.01$), therefore degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity ($\varepsilon = 0.86$). A significant main effect was found for group (F (1, 89) = 5.09, $p = 0.027$) as the MetS group took more moves to solve each of the three-, four-, and five-move problems. Significant main effect was also found for mean moves (three-, four-, five-move problems; F (1.71, 152.24) = 12.24, $p < 0.01$), illustrating that as the difficulty level of the problem increased from a three-move to five-move problem, more moves were needed by both groups to solve the problems successfully. However, there was no interaction between group and mean moves.

Spatial working memory

Between-participants ANOVA showed a trend for SWM strategy (four to eight boxes; $p = 0.101$) but no significant effects were present.

Regression analyses

Presence of MetS, age, education, gender, race, overweightness/obesity, hypertension, hyperlipidemia, and type II diabetes mellitus were entered in a stepwise multiple regression analysis on the CANTAB variables including PAL total trials (eight shapes), IED Errors (blocks 6 and 8), SOC problems solved in minimum moves, SOC sum of moves (three-, four-, five-move problems), and SWM strategy use (four to eight boxes) separately (Table 3).

PAL total trials (eight shapes) were predicted by the presence of MetS F (1, 93) = 4.83, $p < 0.05$ which accounted for approximately 5% of the variance in PAL total trials (eight shapes). IED Errors (Block 6 and 8) was primarily predicted by gender (male) and to a lesser extent by presence of

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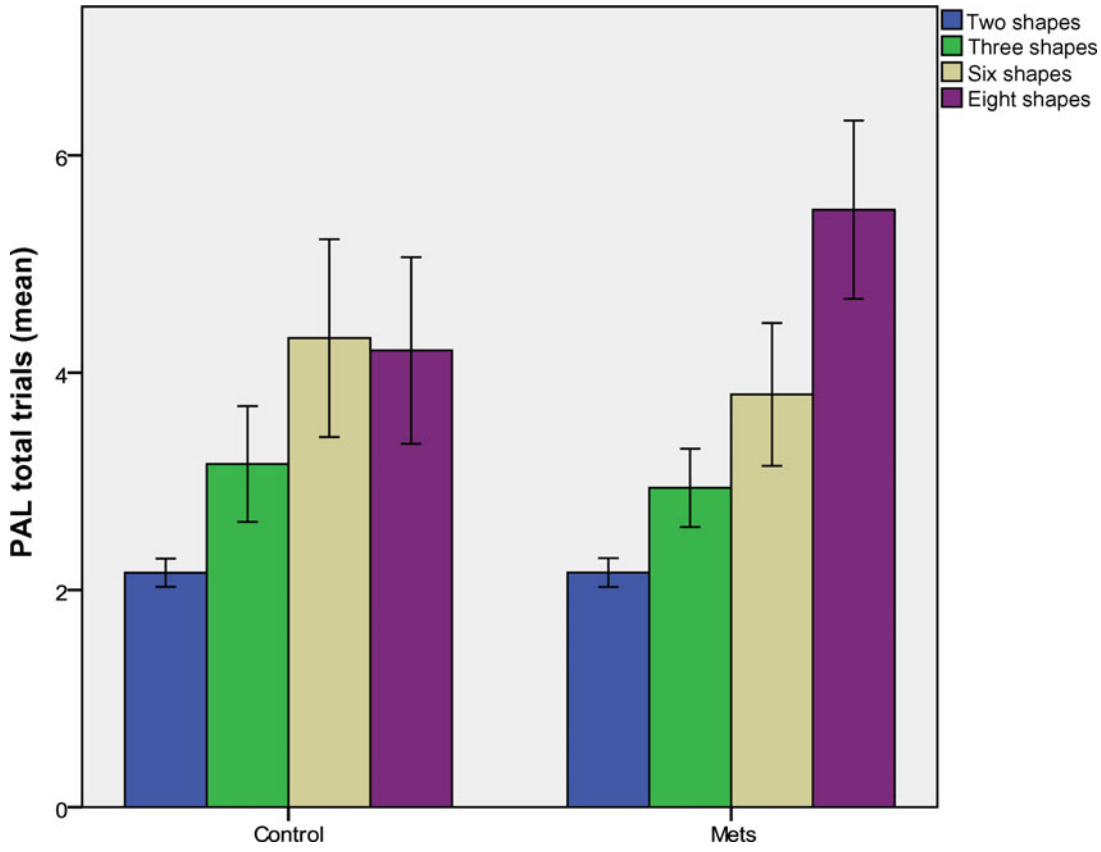


Figure 1. Total trials of MetS and control groups in the paired-associate learning task.

Table 3. Results of stepwise multiple regression analyses for demographic and vascular risk factors that influenced CANTAB performance

	B	SE-B	β	PEARSON r	ΔR^2
PAL total trials (eight shapes)					
Presence of MetS	1.29	0.59	0.222*	0.222	0.049
$R^2 = 0.049$, adjusted $R^2 = 0.039$					
IED sum of Errors (blocks 6 and 8)					
Male	− 5.56	2.07	− 0.262*	− 0.268	0.069
Hyperlipidemia	4.36	2.13	0.199*	0.206	0.040
$R^2 = 0.109$, adjusted $R^2 = 0.090$					
SOC problems solved in minimum moves					
Education level	0.19	0.05	0.325*	0.355	0.124
Hypertension	− 1.22	0.41	− 0.272*	− 0.299	0.096
Chinese	1.28	0.49	0.238*	0.284	0.055
$R^2 = 0.275$, adjusted $R^2 = 0.251$					
SOC sum of moves (3-move, 4-move, 5-move problems)					
Chinese	− 1.93	0.54	− 0.300*	− 0.365	0.133
Education level	− 0.18	0.06	− 0.265*	− 0.351	0.123
Hypertension	1.47	0.45	0.274*	0.354	0.069
Male	− 1.27	0.46	− 0.238*	− 0.334	0.053
$R^2 = 0.379$, adjusted $R^2 = 0.351$					
SWM strategy (four to eight boxes)					
Hypertension	3.11	0.99	0.309*	0.309	0.095
$R^2 = 0.095$, adjusted $R^2 = 0.086$					

*$p < 0.05$.
B = Unstandardized Beta coefficients; SE-B = Standard Error of Beta coefficients; CANTAB = Cambridge Neuropsychological Test Automated Battery; PAL = paired-associate learning; IED = intra-extra dimensional set shift; SOC = stockings of Cambridge; SWM = spatial working memory.

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hyperlipidemia F (2, 94) = 5.75, $p < 0.05$ which accounted for approximately 7% and 4% of the unique variance respectively. SOC problems solved in minimum moves was predicted by education level and hypertension, and to a lesser extent by race (Chinese) F (3, 91) = 11.53, $p < 0.05$ which accounted for approximately 12%, 10% and 6% of the variance respectively. In the same vein, SOC sum of moves was primarily predicted race (Chinese) and education level, and to a lesser extent by hypertension and gender (male) F (4, 91) = 13.87, $p < 0.05$ which accounted for approximately 13%, 12%, 7%, and 5% of the variance. SWM strategy use was predicted by the presence of hypertension only, $F(1, 94) = 9.91$, $p < 0.05$, which accounted for approximately 10% of the variance in SWM strategy use.

Discussion

The main objective of the study was to determine the neuropsychological profile of MetS in a mixed Asian sample using a sensitive neuropsychological test battery. After adjustment of possible confounders (race, gender, education level), MetS participants consistently performed more poorly in the domains of memory and executive functioning but such deficits were subtle and only present at higher levels of cognitive processing and task difficulty. For example, in the PAL test, above chance differences occurred only at the highest difficulty level (eight shapes). MetS participants required more trials to successfully complete the level indicating deficits in non-verbal learning and learning visual memory. This is in accordance with preceding studies reporting comparatively worse new learning and poorer recall amongst MetS individuals compared with controls (Dik *et al.*, 2007; Hassenstab *et al.*, 2010) although we tested participants with visuospatial memory tests.

Executive function was also impaired as MetS participants showed consistently lower performance compared with controls. First, in the IED test, MetS participants made more errors in the IDS and EDS phases combined with inability to make shifts in mental set to solve problems indicating a reduction in cognitive flexibility. Second, in the SOC test, MetS participants solved fewer problems in the stipulated number of moves and required more moves in order to successfully solve a problem, indicating reduced overall planning accuracy. Third, whilst only a trend, responses on the SWM test suggested that MetS participants had a poorer use of strategy when searching for the blue tokens to complete the task. The results relating to executive abilities of MetS individuals concur with Dik *et al.* (2007) and Hassenstab *et al.* (2010) who found cognitive aspects of fluid intelligence, executive functioning, and overall intellectual functioning to be inversely associated with MetS. Our findings are based on sensitive measures of executive function that point to subtle issues of cognitive flexibility and planning.

Whilst we did not examine the entire gamut of neuropsychological functions, on the whole the findings are in line with most western studies with middle-aged or "young old" cohorts, i.e. individuals in our study were aged 55 years and above, with fewer patients above 75 (mean age = 65 years old; Dik *et al.*, 2007; Ho *et al.*, 2008; Hassenstab *et al.*, 2010), and mirror previous studies which have reported memory and executive function deficits in association with vascular disease. Comparably, Hassenstab and colleagues (2010) reported that MetS patients showed impaired cognitive function in a normal aging study of individuals (mean age = 60.4 years) compared with age- and education-matched controls. Nordlund *et al.* (2007) showed significantly worse performance on tests of attention, visuospatial functions, and executive functions in MCI patients with vascular disease (i.e. hypertension, hyperlipidemia, diabetes mellitus) compared with MCI patients without vascular disease.

Our findings contrast with a number of studies that have failed to establish an association between MetS and impaired cognition. Reports of no association, a decelerated decline, or even better cognitive functioning in older MetS patients have been shown in several studies including the Olmsted study with participants aged between 70 to 89 years (Roberts *et al.*, 2010), the Leiden-85 Plus study with individuals aged 85 years and above (van den Berg, *et al.*, 2007), and the Tuscan (Italy) aged 75 years and above (Laudisio *et al.*, 2008), respectively. The effect we see may be because our study contained "young old" participants who acquire MetS earlier in life. Alternately, many of the more severe MetS patients in older cohort studies may have already progressed to dementia or death from other causes, leaving a relatively intact group under investigation. However, the possibility that Asian patients may develop a more severe form of MetS as a consequence of elevated vascular risk also cannot be ruled out at this stage. Further large-scale studies are required to investigate this possibility.

The second objective of the study was to examine the individual influences of vascular risk and intrademographic factors (age, race, education level) on performance. The presence of MetS by itself exerted a significant influence on PAL performance in terms of total trials but not errors. Because PAL does not permit verbal strategies to

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assist encoding, it is viewed as more sensitive to encoding deficits than other memory tests and has demonstrated ability to detect early learning deficits in a-MCI and AD (Swainson *et al.*, 2001; de Jager *et al.*, 2002; Fowler *et al.*, 2002; Nestor *et al.*, 2004; Mitchell *et al.*, 2009; Junkkila *et al.*, 2012) and discriminate between a-MCI and AD (Hammers *et al.*, 2011; Junkkila *et al.*, 2012). Although previous studies of AD have tended to show impairments expressed in the number of errors rather than trials, this effect may be age related (Lee *et al.*, 2013) and present in the oldest patients (Junkkila *et al.*, 2012), and not as common in midlife. Moreover, in the current data, the effect on number of trials is only apparent at the highest level of difficulty suggesting that it is potentially more subtle than in AD. As such, the inclusion of PAL in future MetS follow-up studies is further underlined.

In addition to the general effect of MetS on associate learning and memory, the presence of hyperlipidemia and hypertension may exert individual effects on executive function caused by cerebrovascular disease and cerebral atrophy. Hyperlipidemia was associated with poorer attentional or set shifting flexibility on the IED task whereas hypertension was consistently associated with reduced spatial planning ability and strategy use on the SOC task. Hyperlipidemia in Caucasians is an early risk factor for Alzheimer's disease and has been associated with impaired memory (Waldstein *et al.*, 1996; Zhang *et al.*, 2005). In contrast, hypertension in Caucasians is linked to impaired executive abilities in adults without dementia (Elias *et al.*, 1993; Panza *et al.*, 2010), and it predicts progression to dementia in older people who demonstrate executive dysfunction but not memory dysfunction (Oveisgharan and Hachinski, 2010), suggesting that executive dysfunction is the primary neuropsychological marker of vasculopathy and possible future decline. Goldstein *et al.* (2008) reported that the presence of hypertension and hyperlipidemia, but not their severity, were related to cognitive performance in AD patients. Both are linked to white matter damage and have been independently associated with smaller prefrontal cortex and underlying white matter volumes as well as increased frontal WMH (Raz *et al.*, 2003; 2007; Yoshita *et al.*, 2006). The association between white matter lesions and progression of brain atrophy (Enzinger *et al.*, 2005; Schmidt *et al.* 2005; Raz *et al* 2007) indicates that cerebral small-vessel disease leads to cognitive impairment through generalized brain atrophy. Further large-scale studies can consider individual contributions of vascular risk factors relative to neuropathology in the context of MetS in terms of both individual and additive effects.

Possible protective factors were present in male gender and education on some tests. For executive abilities, males tended to perform better in the IED and SOC tests, while higher education level was also positively correlated with better performance in the SOC test. Previous studies suggest females with MetS are twice as likely to develop cognitive impairment (Schuur *et al.*, 2010) and demonstrate poorer executive function (Hilal *et al.*, 2013). Whilst males tend to outperform females in spatial tasks at a sample level and this may have influenced the findings, the sample size here is rather small to elicit such trends. The effect may be more due to lower education levels in females than gender per se as previous local studies have shown that poorer neuropsychological test performance in cognitively normal elderly is influenced by the number of education years attained (Lee *et al.*, 2012). In Singapore, those with less than one year and more than six years of education have also shown significant differences in dementia prevalence of 1.9% and 0.4% respectively (Sahadevan *et al.*, 2008). Furthermore, as compared to the Chinese, dementia distribution among the Malays and Indians is 1.9 and 2.3 times higher (Sahadevan *et al.*, 2008). In view of the potential interactive influence of Mets-related cognitive impairment with education, race, and dementia risk, further large-scale studies would be helpful in determining if demographic differences in Mets patients translate to differential risk for dementia across the various strata of Asian societies.

The present study has several limitations. Foremost is the limitation of its cross-sectional design which prohibits causal inferences between MetS and cognitive decline. Second, due to the unselected nature of the sample, there was a preponderance of Chinese participants who show the lowest prevalence of Mets within the Singapore population (Tan *et al.*, 2004; Ho *et al.*, 2008), which suggests genetic, diet, and lifestyle factors could, despite the presence of MetS, offer some protection from cognitive decline. Greater numbers of Malay and Indian participants would have permitted clearer statements regarding the important effect of race on Mets-related cognitive change; hence the present findings in relation to race are highly tentative and require replication in a larger sample. In addition, the effect of the level of control of the individual risk factors of hypertension, dyslipidaemia, diabetes mellitus, and the effects of treatment complications, such as hypoglycaemia, were not studied. In general, the percentages of variance explained by the data are somewhat small and imply that these or other unaccounted variables may contribute more variance that is presently unaccounted for or, alternatively, could reduce

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the strength of the observed associations. Finally, genetic susceptibility and markers of inflammation were not assessed in this study. The $\varepsilon 4$ allele of Apolipoprotein E (APOE-$\varepsilon 4$) is a recognized risk factor for AD and among APOE-$\varepsilon 4$ carriers, inflated risk of cognitive impairment or dementia is associated with hypertension (Carmelli *et al.*, 1998), diabetes mellitus, and hyperlipidemia (Blair *et al.*, 2005). Feng *et al.* (2013) showed in Singaporeans that the principal component of MetS, central obesity, showed increased odds of association with a-MCI but this association was strongest among APOE-$\varepsilon 4$ carriers and at younger age. Similarly, inflammation biomarkers have been linked to a heightened risk of cognitive decline and dementia particularly (C-reactive protein; Dik *et al.*, 2007). Future studies would benefit from the inclusion of both lipid and inflammatory biomarkers.

Conclusion

MetS is a serious health condition that appears to have negative consequences on cognitive function as the brain ages. Asians may be particularly vulnerable to the detrimental impacts of MetS and early detection of subtle neuropsychological abnormalities in older adults without dementia, and effective management of vascular risks will aid in successful aging and preservation of quality of life. Currently, whilst the cure for dementia remains elusive, the only option we have is to target those at risk and take all measures to delay its onset.

Conflict of interest

None.

Description of author's roles

S.L. Collinson supervised the analysis of the data and wrote the paper. R.A. Merchant designed the study and supervised the data collection process. S.J.F. Tong collected the data and assisted with writing the paper. S.S.K. Loh was responsible for the analysis of the data and assisted with writing the paper. S.B. Chionh assisted in the data collection process and provided expert consultation.

Acknowledgments

This study was funded by the Oon Chiew Seng Fellowship grant.

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