Cardiovascular Risk Factors and Memory Function in Nepal: Findings from the Dhulikhel Heart Study

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Abstract

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Background: Although a growing number of studies are focusing their attention on cognitive domains, few studies have been conducted in developing countries. Previous studies have suggested that cardiovascular disease (CVD) risk factors may be related to cognitive health or impairment. In the present study, we assessed the associations of CVD risk factors with short-term memory and working memory function among 352 adults from the city of Dhulikhel in Nepal.

Methods: This cross-sectional study used data from the first wave of the Dhulikhel Heart Study (DHS), which was a population-based cohort study to investigate CVD and its risk factors in Nepal. Information on demographics and self-reported CVD risk factors were collected via home interviews. Blood pressure and Body Mass Index (BMI) were clinically measured by trained technicians. Unadjusted and demographic adjusted linear regression models quantified the correlations between CVD risk factors and the Digit Span Forward (DSF) and the Digit Span Backward (DSB) tests, measures of short-term and working memory, respectively. Binomial and multinomial logistic regression models were used to evaluate the relationship of lowered short-term memory and working memory with CVD risk factors. Sensitivity analyses were performed among participants who had never taken any hypertension treatment.

Results: A total of 32.8% of participants in the DHS (N=352) completed either the DSF or the DSB. In linear regression models adjusted for age, sex, education, ethnicity, and household, diabetes was associated lower DSF scores (Coeff=-0.74, p=0.05); however, hypertension and higher BMI were associated with higher DSF scores (Coeff. of hypertension=0.52, p=0.04; Coeff. of BMI=0.05, p=0.05). Other CVD factors did not result in significant relationships with DSF scores. In binomial logistic regression models, BMI was similarly associated with a reduced risk of lowered short-term memory comparing the lowest quartile of the DSF with the other three quartiles (RR=0.96, 95% CI 0.93-1.00). Former smoking was also associated with the reduced risk of lowered short-term memory (RR=0.57, 95% CI 0.39-0.83). Sensitivity analyses provided similar results although associations were attenuated due to reduced sample size (n=276). In the multinomial logistic regression model comparing the highest quartile with the lowest (worst memory) of the DSF, the relative risk for a one-unit increase in BMI and ≥600 MET min/week physical activity was 0.90 (95% CI 0.83-0.98) and 0.52 (95% CI 0.27-0.98), respectively. Working memory based on the DSB test was not significantly associated with any CVD risk factors in the present study.

Conclusion: Our results suggest that hypertension, diabetes, BMI, smoking history, and physical activity may be associated with short-term memory among Nepalese adults. Results should be considered cautiously due to the cross-sectional design of the study, small sample size and multiple tests performed.

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INTRODUCTION

The incidence and prevalence of dementia increase with age, causing much distress to both aging patients and their families. Globally, the number of dementia cases in 2010 was estimated at 35.6 million.[1] Dementia also significantly affects a person's daily functioning and resulted in 1.7 million deaths in 2013.[2] Thus, there is a great need to further understand risk factors for dementia and develop preventive strategies.

Cardiovascular diseases (CVDs) have been reported to increase the risk of vascular dementia which causes at least twenty percent of dementia cases.[3] Many epidemiological studies have suggested that CVD risk factors, such as hypertension, hyperlipidemia, and smoking, are associated with higher rates of Alzheimer's disease, the most common cause of dementia.[4,5] Memory function is a defining clinical characteristic of Alzheimer's disease and thus could be influenced by CVD risk factors prior to diagnosis of the disease.[6]

The relations of cognitive function with CVD risk factors have been well investigated in the past decade. There is a consensus in the literature that moderate-to-vigorous physical exercise is associated with better cognitive function in both sexes.[7,8] However, inconsistent results exist for other risk factors, such as smoking, obesity, diabetes, and hypertension. One study found diabetes as a strong predictor for lower cognitive function;[9] however, another study did not find evidence of significant cognitive decline during a 20-year follow-up among a large group of patients with type I diabetes.[10] Several studies reported negative or non-significant relationships of elevated BMI with cognitive performance;[9,11] however, another study found that risk of dementia was associated with midlife obesity but inversely associated with late-life obesity.[12] Potential explanations for conflicting results may involve differences in study population, design, and covariates of interest included in each study.

In addition to global cognitive outcomes, it is important to consider relationships between risk factors and specific cognitive domains. The most studied cognitive domains are executive function, processing speed, and memory. Memory is commonly described as an information processing system which consists of sensory processors, short-term memory, and long-term memory.[13] Unlike long-term memory, short-term memory can only hold a small amount of information for a short time, usually several seconds, but it is still very important. Although working memory is often used as a synonym for short-term memory, it should be distinguished because it allows one to not only store information but also to manipulate it. Because memory function can highly affect a person's daily life, more studies are focusing on this specific cognitive domain, such as the Women's Health Initiative Memory Study (WHIMS).[14]

Currently, an epidemiologic transition is occurring globally in low- and middle-income countries (LMICs) in which noncommunicable diseases have replaced infectious diseases causing the greatest burden of disease in both mortality and morbidity. While there is ample evidence that identifying and managing individuals with risk factors for CVD can lead to substantial reduction in heart diseases and stroke, very little is known which CVD risk factors may also be impacting the cognition of older adults in LMICs. The Dhulikhel Heart Study provides a unique opportunity to investigate the relationship of CVD risk factors with cognitive function in a suburban community in Nepal, South Asia. This is the first time that memory function and its risk factors will be evaluated among Nepalese adults. The objectives of this analysis were to investigate associations between multiple CVD risk factors and short-term/working memory and to investigate if hypertension medication modifies results.

METHODS

Study design

We performed a cross-sectional study to investigate the relationship of CVD risk factors with short-term and working memory among suburban Nepalese adults in central Nepal.

Study setting

The present study used data from the DHS, a population-based observational study conducted to explore the epidemiology of CVDs and related risk factors among adult residents living in Dhulikhel in central Nepal. The first wave of the DHS baseline survey was performed from November 2013 to February 2015. Eligible subjects were 18 years of age or older, residing in Dhulikhel over 6 months, not pregnant, and without obvious disability at the time of data collection. A total of 1073 eligible subjects were recruited from 735 randomly selected households and participated in the first survey after providing written informed consent.

Study subjects

In the DHS, all participants received a battery of cognitive tests including the Mini-Mental State Examination (MMSE), the Digit Span Forward (DSF) and the Digit Span Forward (DSB). The present study analyzed 352 participants who completed the DSF or the DSB conducted during the DHS baseline survey.

Data source

Data were primarily obtained from the personal questionnaires administered during the baseline survey gathered during home interviews of eligible DHS participants. Demographics collected by self-report included age (years), gender (male/female), education (in formal educated years), illiteracy (yes/no), and ethnicity (Brahmin/ Chettri, Thakwi, Sanyasi/ Newar/ Magar, Tamang/ Sherpa, Bhote/ Kami, Dami, Sarki). A unique number was assigned to each household for subsequent statistical analysis.

Primary exposures for the present study focused on several modifiable CVD risk factors: hypertension, diabetes, overweight/obesity, former/current smoking, and lack of adequate physical activity. In addition to these categorical variables, metrics used to define them were also investigated, i.e. blood pressure, body mass index (BMI), pack-years, and metabolic equivalent task (MET) minutes per week. Collection of these variables are briefly described below.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained technicians at the home visit using an automatic digital blood pressure device (Microlife, Switzerland). The mean of three measurements was used as a continuous variable for analysis. Hypertension was defined as an SBP ≥140 mmHg or a DBP ≥90 mmHg or participants who reported ever taking antihypertensive medication.[15] Participants with hypertension self-reported their use of antihypertensive medicines.

Diabetes was also self-reported by participants. If a participant believed she/he had ever been told to have diabetes by a doctor, her/his information about diabetes treatment/ advice was collected. Diabetes (yes/no) was considered as a binary variable in our analysis.

Body weight and height were measured using standardized procedures at the home visit. Body mass index (BMI) was categorized as underweight <18.5 kg/m^2, normal 18.5-24.9 kg/m^2, overweight 25.0-29.9 kg/m^2, and obese ≥ 30.0 kg/m^2.[16]

Smoking status of participants was categorized as nonsmokers, former smokers, and current smokers based on self-report. Pack-years, a continuous variable representing lifelong exposure to tobacco, was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person smoked.

Physical activity was measured by the Global Physical Activity Questionnaire during the personal interview and expressed as MET minutes per week.[17] Adequate physical activity was defined as exercising greater than 600 MET minutes per week.

The primary outcomes for the current analyses were short-term memory and working memory which were individually assessed by two neuropsychological tests, the DSF and the DSB[18]. In each test, a span consisted of a specific number of digits starting at 2 digits and increasing by 1 up to a maximum 8 digits in the DSF and 7 digits in the DSB. Participants were allowed two trials at each span length to recall the sequence in normal or converse order. One point was given for each correctly recalled span. If a participant failed twice at a certain span, the test was ended. Final scores were calculated by summing the points. These continuous measures of the DSF and DSB were used to represent participants' short-term memory and working memory, respectively.[18] Scores in the lowest quartile in each test were treated as lowered memory function in our study.

Statistical methods

We described the demographic factors and modifiable CVD risk factors for men and women who completed at least one of the two cognitive tests in the DHS. Counts and percentages were provided for categorical variables; means and standard deviations were provided for continuous variables. Performances on the DSF and DSB were described as mean scores with standard deviations and impaired memory function (lowest quartile of each test).

We used general linear regression models to evaluate the relationships of CVD risk factors with the final score of each test. Model 1 was unadjusted showing the crude associations between the dependent and independent variables. Model 2 adjusted for demographic factors including age, gender, education, and ethnicity to control for the potential confounding. In Model 2, we also clustered households to control the shared environment and/or shared genes among household members. To assess the risk of lowered memory function, we used the binary Poisson regression[19] and multinomial logistic regression models and which were adjusted as in the linear regress models. In binary Poisson regression models, the bottom quartile was compared with the other higher quartiles. In multinomial logistic regression models, the lower three quartiles were compared the top quartile separately. We also performed a sensitivity analysis removing hypertensive patients who were treated from the models mentioned above.

All analyses were performed using STATA version 14.2. Statistical significance was set at $p<0.05$.

RESULTS

Characteristics of study participants

Demographic characteristics of the 196 (55.7%) women and 156 (44.3%) men in the study sample are shown in Table 1. Participants were mainly of Newar ethnicity (58.0%) and were a mean age of 57.0 (±13.9) years. The majority of participants were illiterate (57.4%).

The distributions of modifiable CVD risk factors are also presented by gender in Table 1. The prevalence of hypertension was higher in men (58.3% vs. 44.9%), while the prevalence of diabetes was similar in men (7.4%) and women (5.7%). The two genders shared similar mean BMI (Male: 24.0±4.6, Female: 25.0±4.9) but fewer men were obese (7.1% vs. 16.1%). Compared with women, men were more likely to smoke (63.5% vs. 43.9%) and were exposed to more packs of cigarettes per year (17.9±24.3 vs. 9.51±18.0). Although men were more physically active than women, similar proportions of men and women met the recommended physical activity level of 600 MET minutes per week (Male: 49.4%, Female: 47.5%).

Performances of study participants on Digit Span Tests

352 participants in the DHS completed the DSF but none achieved the full 16 points score. 348 participants completed the DSB, with two participants completing the last span of 7 digits with the full 14 points score. The mean score of the DSF was 5.54 (±2.36) points, and the mean score of the DSB was 3.1 (±2.2) points. Score distributions of the two tests were skewed, and we set the lowest quartile of each test as the cut-off point for lowered memory function. There were 33.81% of participants in the present study with lowered short-term memory with DSF scores equal or less than 4 points.

There were 29.31% of participants with lowered working memory with 0 or 1 point of the DSB. Men in our study performed better than women in both tests: on average, men scored 6.4 (±2.3) points on the DSF and 3.9 (±2.0) points on the DSB; women scored 4.87 (±2.2) points on the DSF and 2.4 (±2.2) points on the DSB.

Factors associated with memory function

Linear regression model

Table 2-a and Table 3-a present the correlations between modifiable CVD risk factors and the scores of the DSF and DSB. Model 1 shows unadjusted linear relationships for hypertension, SBP, DBP, diabetes, BMI, smoking status and pack-years, physical activity and mean MET minutes per week in separated models. Model 2 shows associations adjusted for demographic factors and clustered household.

Hypertension was associated with higher DSF scores after adjusting for age, sex, education, and ethnicity (Coeff.=0.52, p=0.04). Although DBP was associated with higher scores of the DSF (Coeff.=0.03, p=0.002) and the DSB (Coeff.=0.03, p=0.005) in the unadjusted models, the association was not significant after adjusting for potential confounders.

Diabetes had a significantly negative relationship with the DSF. Compared with non-diabetic participants, diabetic participants scored 0.74 points lower (p=0.05) on the DSF after adjusting for demographic factors. No relationship was found between diabetes and the DSB.

BMI was positively associated with scores of the DSF in the unadjusted model (Model 1; Coeff.=0.07, p=0.008) and the demographic adjusted model (Model 2; Coeff.=0.05, p=0.05). Categorically compared to people with normal BMI (18.5-24.9), participants who were overweight (BMI 25.0-29.9) scored 0.52 higher in the DSF (p=0.05) after adjustment for potential confounders. No relationship was found between BMI and the score of DSB.

Smoking history, pack-years, and physical activity were not related to neither short-term memory nor working memory in linear regression models. Coefficients are listed in Table 2a and Table 3a.

Binary Poisson regression model and Multinomial logistic regression model

Table 2-b and Table 3-b show the associations of modifiable CVD risk factors with the risk of short-term memory and working memory. As these outcomes were classified as binary (test scores in the lowest quartile considered positive), we report relative risk (RR) with 95% confidence intervals.

Results in Table 2-b suggest that compared to non-smokers, former smokers had a lower risk of lowered short-term memory after adjusting for potential confounders (adjusted RR= 0.57, 95%CI 0.39-0.83). Higher BMI was also negatively associated with the risk of lowered short-term memory (adjusted RR=0.96, 95%CI 0.93-1.00). Hypertension, SBP, DBP, diabetes, and physical activity were not associated with short-term memory. No relationship was found between any CVD risk factors with the risk of working memory (models in Table 3-b).

Considering participants in different quartiles of scores may have different modifiable CVD risk factors, multinomial logistic regression was used to compare the lower three quartiles with the top quartile of DSF and DSB scores. Relative risks (RR) adjusted for age, sex, education, ethnicity, and household are shown in Table 6 and Table 7. The adjusted RR of being in the bottom quartile of DSF (lowered short-term memory) was 0.43 (95%CI 0.19-0.98) for hypertension, 0.90 (95%CI 0.83-0.98) for one unit increase in BMI, and 0.52 (95%CI 0.27-0.98) for reporting physical activity ≥600 MET min/week. Other CVD risk factors didn't have significant relationships with the RR of lowered short-term memory when comparing the bottom quartile with the top quartile. No significant relationship was found for the DSB.

Medications for hypertension and Sensitivity analysis

One hundred seventy-nine participants had hypertension in our study sample based on blood pressure measurement or by self-report of taking medication. Seventy-six (88.4%) who reported that they took hypertension medications had a mean SBP of 144.3 (±18.8) mmHg and mean DBP of 84.2(±11.2) mmHg. To evaluate results in persons not taking antihypertensives, we performed sensitivity analyses using the models in Table 2-a, 2-

b and Table 3-a, 3-b removing hypertensive patients who were treated from the study sample. Results are shown in Table 4-a, 4-b, 5-a, and 5-b. Diabetes remained negatively associated with DSF scores in the sensitivity analysis (Coeff.=-1.12, p=0.05). However, former smoking was no longer associated with the DSF. MET min/week became negatively associated with the DSB (p=0.03).

Discussion

Digit Span Tests and memory functions

In this study, we investigated CVD risk factors for two specific cognitive domains, short-term memory and working memory, measured by the DSF and the DSB, respectively, in Nepalese adults. We found diabetes, BMI, smoking, and physical activity were associated with the DSF scores. No relationships were found between modifiable CVD risk factors and the DSB scores and sensitivity analyses removing patients on hypertensive medications, produced similar results. While some studies in the literature have concluded that the DSB was better than the DSF to detect major cognitive impairments,[20,21] this was not found in our study. This may be due to either real differences between our sample and those in the other studies, or cultural/language issues involving the ability to understand the test.

Blood pressure and short-term memory

As a well-established risk factor for Alzheimer disease and vascular dementia, hypertension has been found to impair global cognitive function and specific cognitive domains.[6,22,23] Hypertension can induce adaptive structural and functional alternations in cerebral blood vessels to prevent further damage in arterial pressure.[24] These changes may result in cerebral blood flow reduction, white matter damage, brain infarcts, and microbleed and consequently impair cognitive functions organically.[25]

Surprisingly, in the present study, hypertension was associated with better short-term memory function after adjusting demographic factors. Others have also reported this result. A recent study found that patients with higher blood pressure had faster response in the task of measuring executive domain,[26] although the sample size was small (n=96) and was comprised of a unique population (older African American Adults). Another study showed the late onset of hypertension protected patients from dementia but only among the oldest indviduauals.[27] Even though the elevated SBP was associated with impaired attention and working memory in some previous studies,[28,29] no significant association was found between SBP and DBP and digit span test scores in the present study. Additionally, in the Southall and Brent Revisited Study (SABRE), cognitive impairment showed a U-shape association with DBP, but not with SBP.[30] The first two studies mainly focused on adolescents and young adults. The SABRE study was performed among middle-aged adults. We hypothesized that age might modify the relationships between blood pressures and cognitive function. In addition, it is possible that hypertension may reflect unmeasured factors or residual confounding in our study. Measuring socioeconomic status (SES) in LMICs is often difficult and we did not have variables other than education to represent it here. If hypertension reflects families with better diets and healthcare, it is possible that hypertensive participants were actually at higher SES in this sample and may provide an explanation for their better cognitive scores.

Diabetes and short-term memory

In the present study, 15 participants (4.3%) self-reported that they had ever been told to have diabetes by a health care provider. This diabetes prevalence was a little higher than the prevalence in the DHS (2.9%). In our linear regression models, diabetes was significantly associated with lower DSF score. Several large population studies have reported similar results. Diabetes was found to be an independent risk factor for cognitive dysfunction[31], dementia[32], and was associated with cognitive decline over 6 years among middle-aged adults.[33] Researchers hypothesize that diabetes could influence memory function through (1)altering the hippocampal white matter connectivity,[34] (2)impairing gamma oscillation in hippocampal neural network[35], and (3)under expressing a certain microRNA (microRNA-146a in mice) and then upregulating cellular prion protein[36] production which plays a role in short-term memory dysfunction. Currently, most of the hypotheses are tested in animal trials. More studies are needed in human populations to explore the pathogenesis of diabetes introduced memory impairment.

BMI and short-term memory

Current studies report inconsistent associations between BMI and multiple cognitive test results. BMI was not associated with immediate verbal memory in the Tromsø study performed among 5033 stroke-free Norwegians, [31] nor with delayed verbal memory and general cognitive ability in middle aged and old aged populations in other studies.[37,38] However, a literature review found that obesity was a risk factor of not only worse attention, worse executive function, and mild cognitive impairment, but also late-life Alzheimer's disease and other dementia.[39]

In the present study, we found a positive correlation between BMI and short-term memory. This agrees with several other studies in the literature. Gunathilake et. al, reported a weak protective effect of obesity on cognitive performance among people over 55 years old residing in Newcastle, Australia.[40] Ishan et. al, also reported a positive correlation between BMI and attention which was measured by the DSF as our study.[6] In the Cardiovascular Health Study, participants with midlife obesity had a 36% increased risk of dementia after adjusting for demographics and other CVD risk factors (HR: 1.36, 95%CI 0.94-1.95). However, late-life obesity was associated with a reduced risk of dementia (HR: 0.63, 95%CI 0.44 to 0.91).[41] An explanation that has been provided for this involves the multiple symptoms that are often found in persons developing dementia including Alzheimer's disease. As physical symptoms, including weight loss and wasting, often occur concurrently or prior to the development of detectable cognitive changes, lower BMI may be a reflection of these comorbidities.

Smoking and short-term memory

Smoking has been widely investigated as a risk factor for various diseases. In several studies, smoking was found to be associated with the increased risks of dementia, Alzheimer's disease, and vascular dementia.[42–46] A population-based cohort study found that smoking was also associated with worse performances on global cognition and executive function.[47] However, in the present study, former smoking was associated with reduced risks of lowered short-term memory. We suspect this may have a relationship with the important component of tobacco, nicotine. Stephen J. Heishman et. al performed a meta-analysis of the acute effects of nicotine on human performance and found the nicotine could significantly enhance smokers' motor abilities, attention, episodic memory, and working memory.[48] This enhancement was also observed in nicotine-deprived smokers which might be partially due to withdrawal relief.[49] Chronic beneficial effects of nicotine on short-term memory had been observed in a selected mouse model,[50] which needs to be confirmed by population-based studies. As our results were found primarily with former smokers, this association may also reflect other positive lifestyles changes in persons who have decided to quit smoking.

Physical activity and short-term memory

Findings from studies that have assessed associations between physical activity and cognitive function are fairly consistent: adequate physical activity provide benefit to the cognitive performances. One study in the Nurses' Health Study showed that long-term regular physical activity was significantly associated with better global cognition (general cognition, attention, verbal memory, and category fluency) and less cognitive decline among US women aged over 70 years old.[51] An interventional study focusing on the episodic memory also found every additional 1000 kcal/week physical activity improved the mean score of the episodic memory test by 0.44 points, while the sample size of this study was small (n=62) and the intervention only lasted for six months.[52] Another study using a different board of adequate physical activity also found similar results.[8] Based on WHO's recommendation, our study settled 600 MET per week as the cut-off point and only found it was associated with the risk of lowered short-term memory in multinomial logistic regression models. As a very brief set of questions was used to measure physical activity in our study, we believe that a more rigorous instrument should be utilized to better detect the association with memory functions in future studies.

Demographics

Associations between demographic characteristics and dementia have been inconsistent in the literature. Study populations varied across studies from children to the oldest-old. In our study, the age ranged from 17 to 88 with near eighty-five percent of people age over 50. Unlike some studies performed among highly educated populations, our study participants were generally under educated. Females received less education than males and the whole illiteracy rate (57.39%) was higher than that in the DHS (31.70%). Another feature of our study was the ethnic diversity. Participants came from more than ten ethnicities. Most participants were the Newars ethnicity or Brahmins ethnicity, and

27% of participants were ethnic minorities. As we have found no other studies on cognition in a Nepalese sample, differences found between our study and others may be due to the unique demographics of this population. Additional investigations in LMICs are needed to ascertain the impact of these factors on dementia.

Strengths and limitations

To our knowledge, the present study is the first to explore associations of CVD risk factors and memory in Nepalese adults. We measured short-term memory and working memory by DSF and DSB which are tests considered appropriate for illiterate persons.[20] Some studies suggested that the cut-off score of <4 in DSF was sensitive to test mild cognitive impairment.[53] However, we defined the lowered short-term/working memory as receiving scores in the lowest quartiles because of the right skewed distribution of the test scores. Although this approach may have resulted in misclassification, it only attenuated our results toward the null but not change the conclusions.

Our study had several limitations. Since it was a cross sectional study, we were not able to determine the temporal relationship between the exposures and the outcomes. We could not compare the effects of the mid-life exposure and the late-life exposure to CVD risk factors since our analysis was built on the baseline survey of the DHS. Although participants in the first wave of DHS came from randomly selected households in Dhulikhel, Nepal, only a subset completed the two digit span tests. Another limitation included the measurement of some exposures, such as smoking and physical activity, that were self-reported by participants. Other metrics for socioeconomic status, such as the household income, and other baseline diseases not assessed may have introduced confounding in results. In addition, with the limitation of the small sample size and the study design, we were not able to investigate the treatment effect of diabetes, the intervention effect of smoking cessation and the result of weight loss. Longitudinal and interventional studies are needed to better understand these factors.

In summary, we found hypertension, diabetes, BMI, and former smoking potentially related to short-term memory among a sample of suburban Nepalese adults living in Dhulikhel, Nepal. Further large-scale, prospective studies and randomized controlled trials to test the impact of preventive strategies are necessary to confirm these associations, especially in LMIC.

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Table 1. Demographic characteristics and cardiovascular risk factors of 352 adults completing the Digit Span Forward test or Digit Span Backward test in the Dhulikhel Heart Study

Characteristics	**Female (N=196)**	**Male (N=156)**	**Total (N=352)**
Age, n (%) (years)			
<30	10 (5.1)	10 (6.4)	20 (5.7)
30-49	26 (13.3)	16 (10.3)	42 (11.9)
50-69	128 (65.3)	105 (67.3)	233 (66.2)
≥70	32 (16.3)	25 (16.0)	57 (16.2)
mean (SD)	57.3 (±13.8)	56.7 (±14.1)	57.0 (±13.9)
Education, n (%)			
Illiterate/ No education	147 (75.0)	55 (35.3)	202 (57.4)
Primary	24 (12.2)	43 (27.6)	67 (19.0)
2-year secondary	14 (7.1)	31 (19.9)	45 (12.8)
4-year secondary	6 (3.1)	12 (7.7)	18 (5.1)
College or higher	5 (2.6)	15 (9.6)	20 (5.7)
Years of formal education, mean (SD)	1.8 (±3.9)	5.7 (±5.3)	3.5 (±5.0)
Ethnicity, n (%)			
Newar	112 (57.1)	92 (59.0)	204 (58.0)
Brahmin	29 (14.8)	24 (15.4)	88 (15.1)
Chettri/Thakwi/Savyas	15 (7.7)	20 (12.8)	35 (9.9)
Magar/Tamang	30 (15.3)	18 (11.5)	48 (13.6)
Others	10 (5.1)	2 (1.3)	12 (3.4)
Hypertension, n (%)	88 (44.9)	91 (58.3)	179 (50.9)
SBP, mean (SD)	130.1 (±20.8)	137.4 (±21.8)	133.3 (±21.5)
DBP, mean (SD)	79.8 (±10.9)	86.1 (±12.3)	82.6 (±11.9)
Diabetes, n (%)	7 (5.7)	8 (7.4)	15 (6.5)
BMI kg/m^2, n (%)			
Underweight (<18.5)	15 (7.8)	7 (4.5)	22 (6.3)
Normal (18.5-24.9)	88 (45.6)	95 (61.3)	183 (52.6)
Overweight (25.0-29.9)	59 (30.6)	43 (27.1)	101 (29.0)
Obese (≥30.0)	31 (16.1)	10 (7.1)	42 (12.1)
mean BMI (SD)	25.0 (±4.9)	24.0 (±4.6)	24.6 (±4.7)
Smoking, n (%)			
Never	110 (56.1)	57(36.5)	167 (47.4)
Former	37 (18.9)	44(28.2)	81 (23.0)
Current	49 (25.0)	55(35.3)	104 (29.6)
Pack years, mean (SD)	9.5 (±18.0)	17.90(±24.3)	13.2 (±21.4)
Physical Activity, n (%)			
<600 MET min/week	103 (52.6)	79 (50.6)	182 (51.7)
≥600 MET min/week	93 (47.5)	77 (49.4)	170 (48.3)
Mean MET min/week (SD)	1640.6 (2711.2)	2687.1 (4789.5)	2104.4 (3805.8)

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; MET, metabolic equivalent task.

Table 2-a. Associations between cardiovascular risk factors with short-term memory* (as measured continuously by Digit Span Forward) in 352 participants of the Dhulikhel Heart Study. Model coefficients (Coeff.), standard errors (SE), and p-values (p) ** are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	Coeff. (SE)	p	Coeff. (SE)	p
Hypertension	179	0.39 (0.25)	0.13	0.52 (0.25)	**0.04**
SBP	352	0.01 (0.01)	0.09	0.01 (0.01)	0.12
DBP	352	0.03 (0.01)	**0.002**	0.01 (0.01)	0.37
Diabetes	15	-0.71 (0.62)	0.26	-0.74 (0.38)	**0.05**
BMI Categories					
<18.5	22	-1.12 (0.53)	**0.04**	-0.54 (0.33)	0.11
18.5-24.9	183	Ref			
25.0-29.9	101	0.69 (0.29)	**0.02**	0.52 (0.26)	**0.05**
>30.0	42	0.37 (0.40)	0.35	0.50 (0.33)	0.13
BMI Value	348	0.07 (0.03)	**0.008**	0.05 (0.02)	**0.05**
Smoking					
Never	167	Ref			
Former	81	-0.05 (0.32)	0.87	0.44 (0.29)	0.13
Current	104	-0.43 (0.30)	0.14	0.09 (0.28)	0.75
Pack-years	352	-0.01 (0.01)	0.17	0.00 (0.00)	0.78
Physical activity					
≥600 MET min/week	170	0.40 (0.25)	0.12	0.35 (0.19)	0.07
MET min/week	352	<0.01 (0.00)	0.88	<0.01 (0.00)	0.93

* Models were analyzed using multiple linear regression.

**P value ≤ 0.05 were in bold.

#Adjusted for sex, age in years, formal educated years, ethnicity, and household.

Table 2-b. Associations between cardiovascular risk factors and risk of lowered short-term memory* (as measured by binary Digit Span Forward test) in 352 participants of the Dhulikhel Heart Study. Relative risks (RR), 95% confidence intervals (95% CI), and p-values (p)** are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	RR (95% CI)	p	RR (95% CI)	p
Hypertension	179	0.78 (0.58-1.04)	0.09	0.76 (0.57-1.01)	0.06
SBP	352	0.99 (0.99-1.00)	0.08	1.00 (0.99-1.00)	0.18
DBP	352	0.99 (0.98-1.00)	**0.03**	1.00 (0.99-1.01)	0.92
Diabetes	15	0.78 (0.33-1.83	0.57	0.84 (0.38-1.86)	0.66
BMI Categories					
<18.5	22	1.21 (0.73-1.98)	0.46	1.00 (0.65-1.53)	0.99
18.5-24.9	183	Ref			
25.0-29.9	101	0.68 (0.47-1.00)	**0.05**	0.73 (0.52-1.04)	0.08
>30.0	42	0.76 (0.45-1.27)	0.29	0.72 (0.44-1.18)	0.19
BMI Value	348	0.96 (0.92-0.99)	**0.01**	0.96 (0.93-1.00)	**0.04**
Smoking					
Never	167	Ref			
Former	81	0.72 (0.47-1.12)	0.15	0.57 (0.39-0.83)	**0.003**
Current	104	1.18 (0.86-1.62)	0.30	0.97 (0.70-1.36)	0.87
Pack-years	352	1.00 (0.99-1.01)	0.98	1.00 (0.99-1.00)	0.27
Physical activity					
≥600 MET min/week	170	0.86 (0.64-1.16)	0.32	0.90 (0.69-1.18)	0.45
MET min/week	352	1.00 (1.00-1.00)	0.76	1.00 (1.00-1.00)	0.28

* Models were analyzed using binary Poisson regression where 1= the bottom quartile of Digit Span Forward score and 0= top three quartiles.

** P value ≤ 0.05 were in bold.

#Adjusted for sex, age in years, formal educated years, ethnicity, clustered household.

Table 3-a. Association between cardiovascular risk factors and working memory* (as measured continuously by Digit Span Backward) in 348 participants of the Dhulikhel Heart Study. Model coefficients (Coeff.), standard errors (SE), and p-values (p)**are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	Coeff. (SE)	p	Coeff. (SE)	p
Hypertension	179	-0.03 (0.24)	0.91	0.18 (0.22)	0.42
SBP	348	0.00 (0.01)	0.53	0.00 (0.00)	0.43
DBP	348	0.03 (0.01)	**0.005**	0.00 (0.01)	0.58
Diabetes	15	0.28 (0.59)	0.64	0.25 (0.43)	0.56
BMI Categories					
<18.5	21	-0.32 (0.51)	0.53	0.24 (0.60)	0.69
18.5-24.9	180	Ref			
25.0-29.9	101	0.18 (0.28)	0.51	-0.02 (0.19)	0.91
>30.0	42	-0.30 (0.38)	0.44	-0.20 (0.27)	0.45
BMI Value	344	-0.00 (0.03)	0.93	-0.03 (0.02)	0.26
Smoking					
Never	166	Ref			
Former	81	-0.28 (0.30)	0.36	0.16 (0.31)	0.61
Current	101	-0.45 (0.28)	0.11	-0.26 (0.22)	0.24
Pack-years	348	-0.00 (0.01)	0.56	0.00 (0.01)	0.39
Physical activity					
≥600 MET min/week	167	0.18 (0.24)	0.46	-0.04 (0.18)	0.82
MET min/week	348	<-0.01 (0.00)	0.87	<-0.01 (0.00)	0.25

*Models were analyzed using multiple linear regression.

** P value ≤ 0.05 were in bold.

#Adjusted sex, age in years, formal educated in years, ethnicity, and household.

Table 3-b. Associations between cardiovascular risk factors with the risk of lowered working memory* (as measured binary by Digit Span Backward) in 348 participants of the Dhulikhel Heart Study. Relative risks (RR), 95% confidence intervals (95% CI), and p-values (p)** are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	RR (95% CI)	p	RR (95% CI)	p
Hypertension	179	0.94 (0.68-1.31)	0.73	0.87 (0.63-1.21)	0.40
SBP	352	1.00 (0.99-1.00)	0.37	1.00 (0.99-1.00)	0.35
DBP	352	0.98 (0.97-0.99)	**0.005**	1.00 (0.98-1.01)	0.59
Diabetes	15	1.14 (0.55-2.39)	0.72	1.42 (0.75-2.69)	0.28
BMI Categories					
<18.5	22	1.65 (1.00-2.73)	0.05	1.35 (0.77-2.35)	0.29
18.5-24.9	183	Ref			
25.0-29.9	101	0.89 (0.60-1.33)	0.58	0.97 (0.67-1.39)	0.85
>30.0	42	0.99 (0.58-1.68)	0.97	0.90 (0.55-1.48)	0.68
BMI Value	348	0.97 (0.93-1.02)	0.22	0.98 (0.94-1.02)	0.43
Smoking					
Never	167	Ref			
Former	81	1.54 (1.04-2.28)	**0.03**	1.27 (0.87-1.85)	0.22
Current	104	1.31 (0.89-1.95)	0.17	1.19 (0.75-1.88)	0.46
Pack-years	352	1.00 (1.00-1.01)	0.27	1.00 (1.00-1.01)	0.43
Physical activity					
≥600 MET min/week	170	0.82 (0.59-1.14)	0.25	0.90 (0.68-1.19)	0.46
MET min/week	352	1.00 (1.00-1.00)	0.93	1.00 (1.00-1.00)	0.39

* Models were analyzed using binary Poisson regression where 1= the bottom quartile of Digit Span Backward score and 0= top three quartiles.

** P value ≤ 0.05 were in bold.

#Adjusted for sex, age in years, formal educated years, ethnicity, and households.

Table 4-a. Sensitivity analysis of the associations between cardiovascular risk factors and short-term memory* in 276 participants of the Dhulikhel Heart Study not using hypertension medications. Model coefficients (Coeff.), standard errors (SE), and p-values (p)** are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	Coeff. (SE)	p	Coeff. (SE)	p
Hypertension	103	0.30 (0.29)	0.30	0.32 (0.26)	0.23
SBP	276	0.01 (0.01)	0.36	0.00 (0.01)	0.58
DBP	276	0.02 (0.01)	**0.04**	0.01 (0.01)	0.59
Diabetes	7	-1.06 (0.91)	0.24	-1.12 (0.55)	**0.05**
BMI Categories					
<18.5	22	-1.01 (0.53)	0.06	-0.50 (0.34)	0.14
18.5-24.9	153	Ref			
25.0-29.9	77	0.83 (0.33)	**0.01**	0.49 (0.29)	0.09
>30.0	20	0.61 (0.55)	0.27	0.14 (0.49)	0.78
BMI Value	272	0.09 (0.03)	**0.003**	0.04 (0.03)	0.20
Smoking					
Never	129	Ref			
Former	53	-0.43 (0.38)	0.26	0.14 (0.34)	0.69
Current	94	-0.84 (0.32)	**0.009**	-0.18 (0.33)	0.58
Pack-years	276	-0.01 (0.01)	**0.04**	-0.00 (0.00)	0.57
Physical activity					
≥600 MET min/week	135	0.24 (0.29)	0.39	0.25 (0.22)	0.25
MET min/week	276	-0.00 (0.00)	0.68	<0.01 (0.00)	0.71

*Models were analyzed using multiple linear regression.

** P value ≤ 0.05 were in bold.

#Adjusted sex, age in years, formal educated in years, ethnicity, and household.

Table 4-b. Sensitivity analysis of the associations between cardiovascular risk factors and lowered short-term memory* in 276 participants of the Dhulikhel Heart Study not using hypertension medications. Relative risks (RR), 95% confidence intervals (95% CI), and p-values (p)** are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	RR (95% CI)	p	RR (95% CI)	p
Hypertension	103	0.74 (0.51-1.06)	0.10	0.77 (0.56-1.07)	0.12
SBP	276	0.99 (0.99-1.00)	0.08	0.99 (0.99-1.00)	0.18
DBP	276	0.99 (0.98-1.00)	0.06	1.00 (0.99-1.01)	0.78
Diabetes	7	1.25 (0.52-3.00)	0.61	1.38 (0.61-3.12)	0.44
BMI Categories					
<18.5	22	1.18 (0.71-1.94)	0.52	1.02 (0.66-1.56)	0.94
18.5-24.9	153	Ref			
25.0-29.9	77	0.64 (0.41-0.99)	**0.05**	0.76 (0.52-1.13)	0.18
>30.0	20	0.65 (0.30-1.42)	0.28	0.88 (0.45-1.74)	0.72
BMI Value	272	0.95 (0.91-0.98)	**0.005**	0.97 (0.93-1.01)	0.10
Smoking					
Never	129	Ref			
Former	53	0.85 (0.51-1.43)	0.55	0.65 (0.41-1.05)	0.08
Current	94	1.41 (0.99-1.99)	**0.05**	1.08 (0.73-1.59)	0.69
Pack-years	276	1.00 (1.00-1.01)	0.46	1.00 (0.99-1.01)	0.68
Physical activity					
≥600 MET min/week	135	0.86 (0.62-1.20)	0.38	0.89 (0.65-1.22)	0.48
MET min/week	276	1.00 (1.00-1.00)	0.45	1.00 (1.00-1.00)	0.15

* Models were analyzed using binary Poisson regression where 1= the bottom quartile of Digit Span Backward score and 0= top three quartiles.

** P value ≤ 0.05 were in bold.

#Adjusted for sex, age in years, formal educated years, ethnicity, and households.

Table 5-a. Sensitivity analysis of the associations between cardiovascular risk factors and working memory* in 272 participants of the Dhulikhel Heart Study not using hypertension medications. Model coefficients (Coeff.), standard errors (SE), and p-values are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	Coeff. (SE)	p	Coeff. (SE)	p
Hypertension	103	0.21 (0.28)	0.46	0.28 (0.26)	0.29
SBP	272	0.01 (0.01)	0.39	0.01 (0.01)	0.29
DBP	272	0.02 (0.01)	**0.04**	0.01 (0.01)	0.30
Diabetes	7	0.42 (0.87)	0.63	0.50 (0.61)	0.41
BMI Categories					
<18.5	21	-0.32 (0.53)	0.55	0.17 (0.59)	0.78
18.5-24.9	150	Ref			
25.0-29.9	77	0.37 (0.32)	0.24	0.01 (0.22)	0.98
>30.0	20	0.22 (0.54)	0.68	-0.34 (0.37)	0.36
BMI Value	268	0.03 (0.03)	0.28	-0.03 (0.03)	0.38
Smoking					
Never	128	Ref			
Former	53	-0.19 (0.37)	0.61	0.32 (0.43)	0.46
Current	91	-0.76 (0.31)	**0.01**	-0.35 (0.24)	0.14
Pack-years	272	-0.01 (0.01)	0.39	0.00 (0.01)	0.42
Physical activity					
≥600 MET min/week	132	-0.01 (0.28)	0.99	-0.14 (0.21)	0.49
MET min/week	272	-0.00 (0.00)	0.23	-0.00 (0.00)	**0.03**

*Models were analyzed using multiple linear regression.

** P value ≤ 0.05 were in bold.

#Adjusted sex, age in years, formal educated in years, ethnicity, and household.

Table 5-b. Sensitivity analysis of the associations between cardiovascular risk factors and risk of lowered working memory* in 272 participants of the Dhulikhel Heart Study not using hypertension medications. Relative risks (RR), 95% confidence intervals (95% CI), and p-values (p)** are shown.

		Unadjusted Model 1		Adjusted Model 2#	
	N	RR (95% CI)	p	RR (95% CI)	p
Hypertension	103	0.80 (0.53-1.21)	0.30	0.83 (0.55-1.24)	0.35
SBP	272	0.99 (0.98-1.00)	0.25	1.00 (0.98-1.01)	0.40
DBP	272	0.98 (0.96-1.00)	**0.03**	0.99 (0.97-1.01)	0.50
Diabetes	7	1.02 (0.31-3.36)	0.97	1.36 (0.42-4.35)	0.61
BMI Categories					
<18.5	21	1.74 (1.04-2.93)	**0.04**	1.45 (0.85-2.50)	0.18
18.5-24.9	150	Ref			
25.0-29.9	77	0.90 (0.56-1.44)	0.67	1.11 (0.71-1.74)	0.64
>30.0	20	0.73 (0.29-1.83)	0.50	1.05 (0.46-2.37)	0.91
BMI Value	268	0.95 (0.90-1.00)	**0.05**	0.98 (0.93-1.04)	0.47
Smoking					
Never	128	Ref			
Former	53	1.70 (1.04-2.78)	**0.04**	1.46 (0.89-2.39)	0.14
Current	91	1.56 (1.00-2.44)	**0.05**	1.27 (0.74-2.19)	0.39
Pack-years	272	1.00 (1.00-1.01)	0.14	1.00 (1.00-1.01)	0.28
Physical activity					
≥600 MET min/week	132	1.01 (0.69-1.48)	0.98	1.07 (0.75-1.52)	0.71
MET min/week	272	1.00 (1.00-1.00)	0.36	1.00 (1.00-1.00)	0.09

* Models were analyzed using binary Poisson regression where 1= the bottom quartile of Digit Span Backward score and 0= top three quartiles.

** P value ≤ 0.05 were in bold.

#Adjusted for sex, age in years, formal educated years, ethnicity, and households.

Table 6. Associations between cardiovascular risk factors and short-term memory using multinomial logistic regression method* to compare the lower three quartiles with the top quartile of Digit Span Forward/Backward scores. Relative risks (RR), 95% confidence intervals (95% CI), and p-values (p)** are shown.

	Digit Span Forward scores					
	2nd Quartile		3rd Quartile		4th Quartile	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Hypertension	0.64(0.30-1.36)	0.24	0.76(0.31-1.83)	0.54	0.43(0.19-0.98)	**0.04**
SBP	1.00(0.98-1.01)	0.86	1.00(0.98-1.01)	0.64	0.99(0.97-1.01)	0.19
DBP	0.99(0.96-1.02)	0.43	0.98(0.95-1.02)	0.30	0.99(0.96-1.02)	0.43
Diabetes	0.39(0.03-5.18)	0.48	6.39(1.05-38.87)	**0.04**	1.86(0.28-12.23)	0.52
BMI Categories						
<18.5#	-	-	-	-	-	-
18.5-24.9	Ref					
25.0-29.9	0.81(0.41-1.62)	0.56	0.58(0.22-1.53)	0.27	0.42(0.18-0.95)	**0.04**
>30.0	0.43(0.13-1.42)	0.17	0.62(0.19-1.99)	0.42	0.31(0.09-1.08)	0.07
BMI Value	0.97(0.90-1.05)	0.48	0.94(0.86-1.03)	0.16	0.90(0.83-0.98)	**0.02**
Smoking						
Never					Ref	
Former	1.14(0.45-2.89)	0.78	1.07(0.36-3.19)	0.91	0.41(0.16-1.05)	0.06
Current	0.73(0.30-1.75)	0.48	0.82(0.32-2.09)	0.68	0.78(0.30-2.02)	0.62
Pack-years	1.02(1.00-1.04)	**0.02**	1.01(1.00-1.03)	0.14	1.01(0.99-1.03)	0.40
Physical activity						
≥600 MET min/week	0.61(0.32-1.17)	0.14	0.54(0.27-1.08)	0.08	0.52(0.27-0.98)	**0.04**
MET min/week	1.00(1.00-1.00)	**0.03**	1.00(1.00-1.00)	0.06	1.00(1.00-1.00)	0.42

* Adjusted for demographic factors including age, sex, education, ethnicity, and household.

** P value ≤ 0.05 are shown in bold.

#None in the top quartile of DSF scores has BMI less than 18.5. Only 2 people in the top quartile of DSB scores have BMI less than 18.5.

Table 7. Associations between cardiovascular risk factors and working memory using multinomial logistic regression method[*] to compare the lower three quartiles with the top quartile of Digit Span Forward/Backward scores. Relative risks (RR), 95% confidence intervals (95% CI), and p-values (p)[**] are shown.

	Digit Span Backward scores					
	2nd Quartile		3rd Quartile		4th Quartile	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Hypertension	0.90(0.35-2.35)	0.83	0.63(0.22-1.83)	0.40	0.54(0.19-1.53)	0.24
SBP	1.00(0.98-1.02)	0.92	0.99(0.97-1.01)	0.49	0.99(0.97-1.01)	0.30
DBP	1.02(0.99-1.06)	0.16	1.00(0.96-1.04)	0.99	1.00(0.95-1.04)	0.88
Diabetes	0.69(0.12-3.86)	0.68	0.40(0.06-2.69)	0.35	0.91(0.16-5.10)	0.91
BMI Categories						
<18.5[#]	0.37(0.04-3.00)	0.35	0.45(0.04-4.79)	0.51	0.76(0.07-8.03)	0.82
18.5-24.9	Ref					
25.0-29.9	1.31(0.60-2.85)	0.50	0.89(0.32-2.48)	0.82	0.91(0.32-2.59)	0.86
>30.0	1.56(0.38-6.49)	0.54	2.03(0.42-9.92)	0.38	1.51(0.30-7.60)	0.62
BMI Value	1.08(0.99-1.18)	0.10	1.08(0.96-1.21)	0.19	1.04(0.92-1.19)	0.51
Smoking						
Never						
Former	0.74(0.23-2.38)	0.61	0.42(0.11-1.67)	0.22	0.84(0.21-3.41)	0.81
Current	0.63(0.23-1.70)	0.36	1.29(0.43-3.85)	0.65	1.50(0.42-5.34)	0.53
Pack-years	0.98(0.96-1.00)	**0.03**	0.98(0.96-1.00)	0.07	0.99(0.96-1.01)	0.17
Physical activity						
≥600 MET min/week	0.95(0.40-2.28)	0.92	0.92(0.36-2.35)	0.86	0.73(0.28-1.91)	0.53
MET min/week	1.00(1.00-1.00)	0.48	1.00(1.00-1.00)	0.73	1.00(1.00-1.00)	0.99

* Adjusted for demographic factors including age, sex, education, ethnicity, and household.

** P value ≤ 0.05 are shown in bold.

#None in the top quartile of DSF scores has BMI less than 18.5. Only 2 people in the top quartile of DSB scores have BMI less than 18.5.