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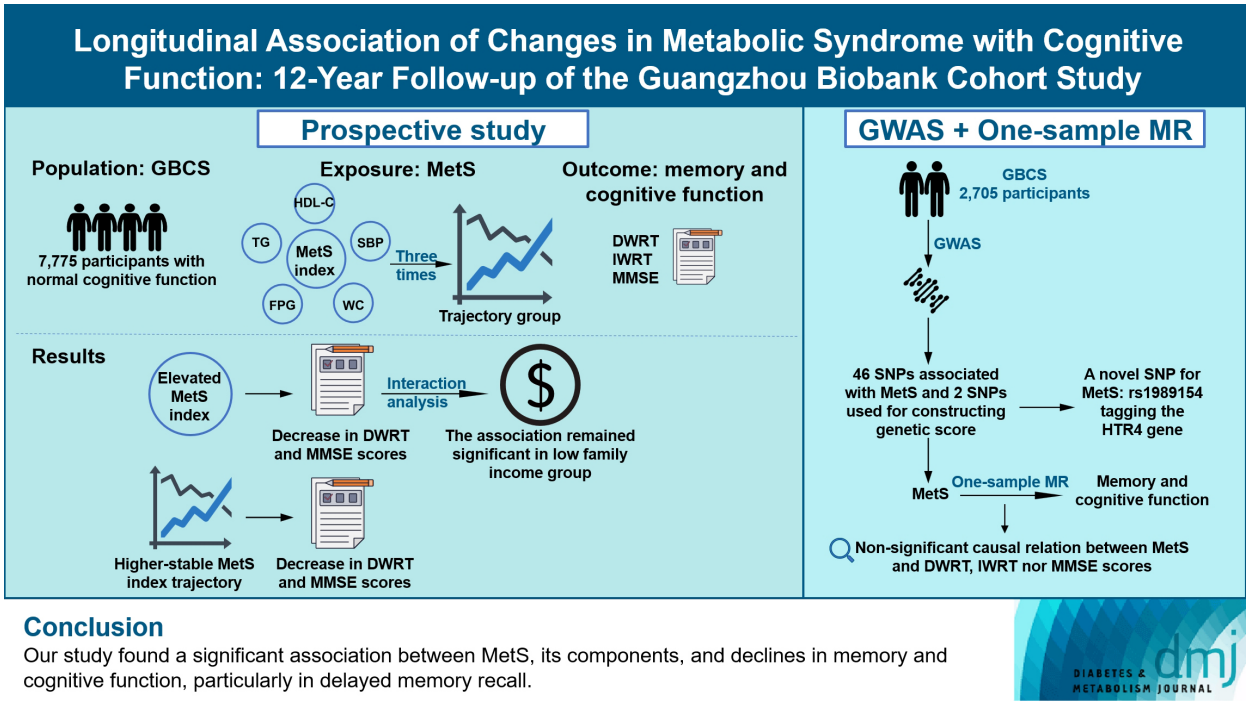

Conclusion

Our study found a significant association between MetS, its components, and declines in memory and cognitive function, particularly in delayed memory recall.

Highlights

- **Changes in MetS and cognitive decline were studied in both prospective and MR studies.**
- **Greater MetS was tied to faster cognitive decline, especially in delayed memory recall.**
- **The link between MetS and cognitive decline was mainly seen in the low-income group.**
- **The GWAS of MetS found significant SNPs in the Chinese population.**

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Longitudinal Association of Changes in Metabolic Syndrome with Cognitive Function: 12-Year Follow-up of the Guangzhou Biobank Cohort Study

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Background: The association of changes in metabolic syndrome (MetS) with cognitive function remains unclear. We explored this association using prospective and Mendelian randomization (MR) studies.
Methods: MetS components including high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), waist circumference (WC), fasting plasma glucose (FPG), and triglycerides were measured at baseline and two follow-ups, constructing a MetS index. Immediate, delayed memory recall, and cognitive function along with its dimensions were assessed by immediate 10-word recall test (IWRT) and delayed 10-word recall test (DWRT), and mini-mental state examination (MMSE), respectively, at baseline and follow-ups. Linear mixed-effect model was used. Additionally, the genome-wide association study (GWAS) of MetS was conducted and one-sample MR was performed to assess the causality between MetS and cognitive function.
Results: Elevated MetS index was associated with decreasing annual change rates (decrease) in DWRT and MMSE scores, and with decreases in attention, calculation and recall dimensions. HDL-C was positively associated with an increase in DWRT scores, while SBP and FPG were negatively associated. HDL-C showed a positive association, whereas WC was negatively associated with increases in MMSE scores, including attention, calculation and recall dimensions. Interaction analysis indicated that the association of MetS index on cognitive decline was predominantly observed in low family income group. The GWAS of MetS identified some genetic variants. MR results showed a non-significant causality between MetS and decrease in DWRT, IWRT, nor MMSE scores.
Conclusion: Our study indicated a significant association of MetS and its components with declines in memory and cognitive function, especially in delayed memory recall.

Keywords: Cognition; Mendelian randomization analysis; Metabolic syndrome; Prospective studies

INTRODUCTION

Due to population aging worldwide, dementia has become a primary public health problem, including a set of symptoms such as memory loss. Notably, no effective treatment for dementia has been developed to date. Hence, as the recent authority report suggested [1], identification and early intervention on some modifiable factors could delay or even prevent the risk of

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cognitive decline, especially in older people.

Abnormal metabolism has been implicated in the pathogenesis of dementia [2,3]. However, the effect of metabolic syndrome (MetS), which is characterized by a set of dysfunctions including dyslipidemia, hypertension, hyperglycemia, and obesity [4], on cognitive decline remains inconclusive. Most cohort studies used a dichotomous classification of baseline MetS status showing inconsistent associations with cognitive decline, i.e., positive [5,6], negative [7], or null [8,9]. This dichotomous approach has limitations. For example, slight variations in component values can alter MetS classification, particularly in participants with borderline values. Additionally, treating MetS as a dichotomous variable reduces the statistical power. To date, only one cross-sectional study, which measured the MetS index, showed that higher MetS index scores were associated with lower cognitive performance [10]. Furthermore, recent studies indicated that the levels of MetS components, such as lipids and glucose, could fluctuate throughout the life course, even in older age [11,12]. Therefore, examining the long-term trajectory of both MetS and its components and exploring their associations with cognitive decline is warranted.

Mendelian randomization (MR), which employs genetic instrumental variables (IV), is useful in reducing confounding and reverse causality in observational studies, especially when randomized controlled trials are infeasible [13]. The proliferation of genome-wide association studies (GWAS) has helped in identifying significant single nucleotide polymorphisms (SNPs) associated with complex phenotypes, which can be used as IV in MR analyses. Previous GWAS of MetS, categorized as case and control, predominantly focused on participants of European ancestry [14,15]. Among these, one study also performed an MR analysis, which found no association between MetS and dementia [14]. Additionally, several studies based on Asian population conducted GWAS of MetS [16], but the causal association between MetS and cognitive function remains unexplored, highlighting the need for further investigation considering the significant impact of ethnic differences.

Therefore, our study aims to examine the prospective associations of changes in MetS, expressed as an index, and its components with cognitive decline in middle-aged and older Chinese. We also explored potential modifiers of the associations. Furthermore, we conducted a GWAS of MetS, categorized as case and control, within a homogeneous Chinese cohort and used MR analysis to assess the potential causal link between MetS and cognitive function.

METHODS

Study sample and setting

The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the Guangzhou Biobank Cohort Study (GBCS) and all participants gave written, informed consent before participation (IRB No. 20030210). All methods were performed in accordance with the relevant guidelines and regulations. Details of the GBCS have been reported previously [17,18]. Briefly, the GBCS is a three-way collaboration among Guangzhou Twelfth People's Hospital and the Universities of Hong Kong and Birmingham. Participants were drawn from the Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE), from September 2003 to January 2008. About 7% of Guangzhou residents aged 50 years or above were included in the GHHARE.

All surviving participants were invited to return for the first (March 2008 to December 2012) and second follow-up examinations (March 2013 to January 2020). Both the baseline and follow-up examinations included a face-to-face, computer-assisted interview conducted by trained nurses to collect information on demographic characteristics, lifestyle factors, and family and personal medical history. Anthropometric and clinical parameters such as fasting plasma glucose (FPG), blood pressure and lipids were measured. The follow-up questionnaire and clinical and laboratory examinations were largely similar to those conducted at baseline. The reliability of the questionnaire was tested by randomly recalling 200 participants for re-interview and the results were satisfactory [17].

MetS measurement

MetS components including high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), waist circumference (WC), FPG, and triglycerides (TG) were measured at baseline and during two follow-up examinations. Levels of SBP, in mm Hg, were recorded as the mean of the last two readings from three measurements, taken using a digital sphygmomanometer (Omron 705CP, Omron, Kyoto, Japan) [19]. Levels of HDL-C, FPG, and TG, in mmol/L, were measured using a Roche COBAS automatic biochemical analyzer (Basel, Switzerland) in the clinical laboratory of the Guangzhou Twelfth People's Hospital [19]. Levels of WC, in cm, were measured horizontally around the narrowest part of the torso, between the lowest ribs and the iliac crest [19]. To reduce bias from dichotomous variable in the observational study, we constructed a

MetS index based on these five components [20,21]. Each component was standardized based on the mean and standard deviation (SD) at baseline. As lower levels of HDL-C indicate poorer health, HDL-C scores were reversed after standardization. The MetS index was derived as the mean of these five standardized variables [20,21]. Furthermore, patterns of changes in the MetS index and its components were all classified according to trajectory analysis.

In the GWAS and MR analysis, MetS was used as a dichotomous variable (case/control). The standard assessment of MetS status has been previously reported in the GBCS studies [22]. Briefly, the MetS was defined by the presence of ≥3 risk factors, which included raised blood pressure (130/85 mm Hg) or treatment of previously diagnosed hypertension; FPG ≥5.6 mmol/L or treatment of previously diagnosed type 2 diabetes mellitus; TG ≥1.7 mmol/L or treatment for the lipid abnormality; HDL-C <1.0 mmol/L for men or HDL-C <1.3 mmol/L for women, or medication use; and central obesity defined as a WC ≥90 cm for men and ≥80 cm for women.

Memory and cognitive function assessment

Immediate 10-word recall test (IWRT), delayed 10-word recall test (DWRT), and mini-mental state examination (MMSE) were used to assess the immediate, delayed memory recall and cognitive function, respectively, at both baseline and two follow-up examinations, as reported in our previous GBCS papers [18,23]. Greater scores indicated better function and reduction in scores indicated a decline in function. DWRT or IWRT was a test of verbal learning and memory requiring recall a list of ten words. To better fit Chinese culture, the adapted 10-word list included 'letter,' 'ticket,' 'grass,' 'arm,' 'corner,' 'stick,' 'book,' 'stone,' 'chairman,' and 'soy sauce.' During the interview, these 10 words were read out to participants one by one. Then the participants were immediately asked to recall the words. Participants were given one point for each word that they could correctly recall. This process was repeated three times and summed scores for these three recalls were IWRT (0–30). After 5 minutes of answering other questions for distraction, participants were asked to recall as many words as they could remember. The last recall was DWRT (0–10). The total number of words was denoted by IWRT and DWRT scores, respectively. Memory impairment was defined by DWRT scores of less than 4, corresponding to one SD below the mean (mean±SD, 5.5±1.8) [23]. MMSE consisted of 11 items (0–30), as reported in our previous GBCS paper [24]. MMSE can be divided into five dimensions, including orientation (0–10), registration (0–3), attention and calculation (0–5), recall (0–3), and language (0–9) [25]. Poor cognitive function was defined by MMSE scores of less than 25, corresponding to one SD below the mean (mean±SD, 27.5±2.6).

DNA extraction and genotyping

The Guangzhou Biobank contains genetic data from 3,137 participants. DNA was extracted from buffy coat stored at −80°C at the Guangzhou Twelfth People's Hospital, using a standard magnetic bead extraction procedure. DNA concentrations were measured using Nanodrop (Thermo Scientific, Waltham, MA, USA). In cases where the concentrations were below 15 ng/μL, DNA was re-extracted manually using a silica-based column method (Hipure Blood DNA Mini Kit, Magen Biotechnology, Guangzhou, China). For genotyping, we used the Illumina ASA (BeadChip Array Asian Screening Array-24+v1.0 HTS ASAMD-24v1-0, San Diego, CA, USA) genotyping platform (array). The ASA array includes a broad spectrum of pharmacogenomics markers (n=5,588) obtained from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (www.cpicpgx.org) and the Pharmacogenomics Knowledge Base (PharmGKB) database (www.pharmgkb.org). Additional information about the ASA array is available on the official Illumina website (https://www.illumina.com/products/by-type/microarray-kits). Genotyping assays were performed at Guoke Biotechnology Co., LTD in Beijing, China (www.bioguoke.com). Further details regarding DNA extraction, genotyping methods and quality control measures are provided in the Supplementary Methods.

Potential confounders

Baseline sociodemographic, lifestyle and biological factors, self-rated health, and self-reported history of disease and medication were analyzed as potential confounders. Sociodemographic factors included age, sex, education (junior middle or below, senior middle or above), occupation (manual, nonmanual, others), marital status (married, others), and family income (<30,000 Chinese yuan [CNY]/year, ≥30,000 CNY/year; US$1=6.95 CNY). Lifestyle factors included physical activity (inactive, minimally active, active), smoking status (never, ever), and drinking status (never, ever). The biological factor considered was body mass index (BMI). Physical activity was assessed by the International Physical Activity Questionnaire, which was validated in our cohort previously [26]. Addi-

tionally, self-reported health status (poor, very poor) and history of disease and medication use including cardiovascular disease, hyperlipidemia, diabetes, hypertension, and drugs for managing hypertension, glucose and lipids, were assessed by experienced nurses.

Statistical analysis

Conventional observational study

We used the semiparametric group-based trajectory model (GBTM) to identify potential subgroups of participants using the Stata command 'traj.' GBTM, an application of finite mixture modelling, is used to identify groups of participants who share similar developmental trajectories over the entire follow-up period [27]. This method assumes population heterogeneity and the existence of a finite number of distinct groups [27]. Model fit was evaluated using the Bayesian information criterion (BIC) and average posterior probability (AvePP) [12], with a lower BIC and AvePP >0.7 indicating a good fit (Supplementary Table 1). Baseline characteristics by MetS index trajectory groups were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables.

To explore the longitudinal association of MetS index and MetS index trajectory groups with changes in memory and cognitive function as well as the five dimensions of cognitive function over time, we primarily used the linear mixed-effect model with random intercept and slopes. This approach yielded regression coefficients (βs) and 95% confidence intervals (CIs). Interaction terms for MetS index/MetS index trajectory groups and follow-up time (in years) were included in the model, respectively. The estimate for interaction terms indicates the extent of longitudinal association between MetS index/MetS index trajectory groups and annual change rates in scores (score per year) [28]. Additionally, we used the linear mixed-effect model to examine the association of the MetS components and their trajectory groups with changes in memory and cognitive function, and the five dimensions of cognitive function over time, yielding βs and 95% CIs.

In the sensitivity analyses, we tested interactions between the MetS index and potential effect modifiers including sex, age (60, ≥60 years), education (≤junior, ≥senior middle school), and family income (30,000, ≥30,000 CNY/year) by adding the three-way interaction items (i.e., MetS index×follow-up time×sex, age, education, family income) to the models.

GWAS and MR analysis

We initially performed the GWAS of MetS as a case-control using the 'Plink' command in Linux software, setting a genome-wide significance threshold at $P<5\times10^{-6}$. Because the participants in our cohort are all from the same population with better homogeneity, the principal component analysis was not conducted in the present study. Manhattan and quantile-quantile (Q-Q) plots were generated using the R package 'qqmen.' We also assessed Hardy-Weinberg equilibrium and excluded the SNPs that violate this principle. Linkage disequilibrium (LD) was performed to test the correlation among SNPs. If two SNPs showed LD ($r^2\geq0.1$), the variant with a larger *P* value in the GWAS of MetS was excluded [29]. Subsequently, the selected SNPs were aggregated into a genetic score, which served as the IV in the subsequent one-sample MR analysis. Allele scores were calculated based on the dose of the risk allele at each SNP, weighted by the effect size of the corresponding variant and then summed as follows:

$$\text{weighted MetS score} = w1\times SNP_1 + w2\times SNP_2 + \ldots + wn\times SNP_n$$

where *w* represents the weight (i.e., the beta-coefficient of association of the SNP with MetS in GWAS) and SNP is the dosage of MetS-developing alleles at that locus (i.e., 0, 1, or 2 MetS-developing alleles). Moreover, to assess potential weak instrumental bias and the reliability of the IV, we evaluated the F-statistic from the regression of MetS on the MetS genetic score. An F-statistic value greater than 10 indicates a valid genetic instrument, suggesting that the IV is unlikely to be weak [13]. In the one-sample MR analysis, we used a two-stage estimation to investigate the association between the IV, represented by the genetic score, and memory and cognitive function using the R package 'ivtools' [30]. Specifically, in the first stage, the exposure $\widehat{\mathbf{X}}$ was determined by calculating the fitted values from the regression of X on IV. The potential causal effect $\beta_{\widehat{\mathbf{X}}\mathbf{Y}}$ was estimated by regressing Y on $\widehat{\mathbf{X}}$ [30]. All data analysis was conducted using Stata/SE 16.0, R software 4.0.3, and Linux software, with a two-sided $P<0.05$ considered statistically significant.

RESULTS

Of 8,592 participants with all variables of interest, after excluding those with memory impairment or poor cognitive function at baseline ($n=817$), 7,775 participants were included in the current study. Of them, 3,251 participants had the MMSE test.

Furthermore, 2,705 participants, including 742 cases and 1,963 controls, were genotyped and used for the GWAS of MetS. Subsequently, 2,613 participants were used for the one-sample MR analysis of memory function, and 677 participants for the analysis of cognitive function. The mean age of participants at baseline was 59.3±6.1 years, with women constituting 74% of the cohort. The average duration of follow-up was 8.1±1.5 years.

Conventional observational study results

In Fig. 1, the MetS index was classified into low-stable (18.3%), moderate-stable (49.5%), high-stable (28.0%), and higher-stable (4.2%) trajectory groups. Regarding the components of MetS index, HDL-C, SBP, and WC were classified into four trajectory groups, while FPG and TG were into two trajectory groups. HDL-C included low-stable (54.3%), moderate-stable (34.2%), high-stable (7.7%), and moderate-increase (3.8%) trajectory groups. SBP included low-stable (24.5%), moderate-stable (45.8%), high-stable (25.1%), and higher-stable (4.6%) trajectory groups. WC included low-stable (13.4%), moderate-stable (41.9%), high-stable (36.3%), and higher-stable (8.4%) trajectory groups. FPG included low-stable (94.9%) and high-increase (5.1%) trajectory groups. TG included low-stable (95.2%) and high-stable (4.8%) trajectory groups.

Table 1 shows that at baseline, compared to the low-stable MetS index group, the higher-stable group was older and had a greater proportion of men, ever smokers, drinkers, and poor self-rated health. This group also had higher levels of BMI, and had a higher prevalence of cardiovascular disease, hyperlipidemia, diabetes, hypertension, and medication use. Additionally, the higher-stable group had a lower proportion of physically active individuals, lower levels of education, and lower baseline scores in DWRT and IWRT (all $P<0.05$). Similar patterns were found in the high-stable MetS index group, except for a lower proportion of poor self-rated health. No associations were

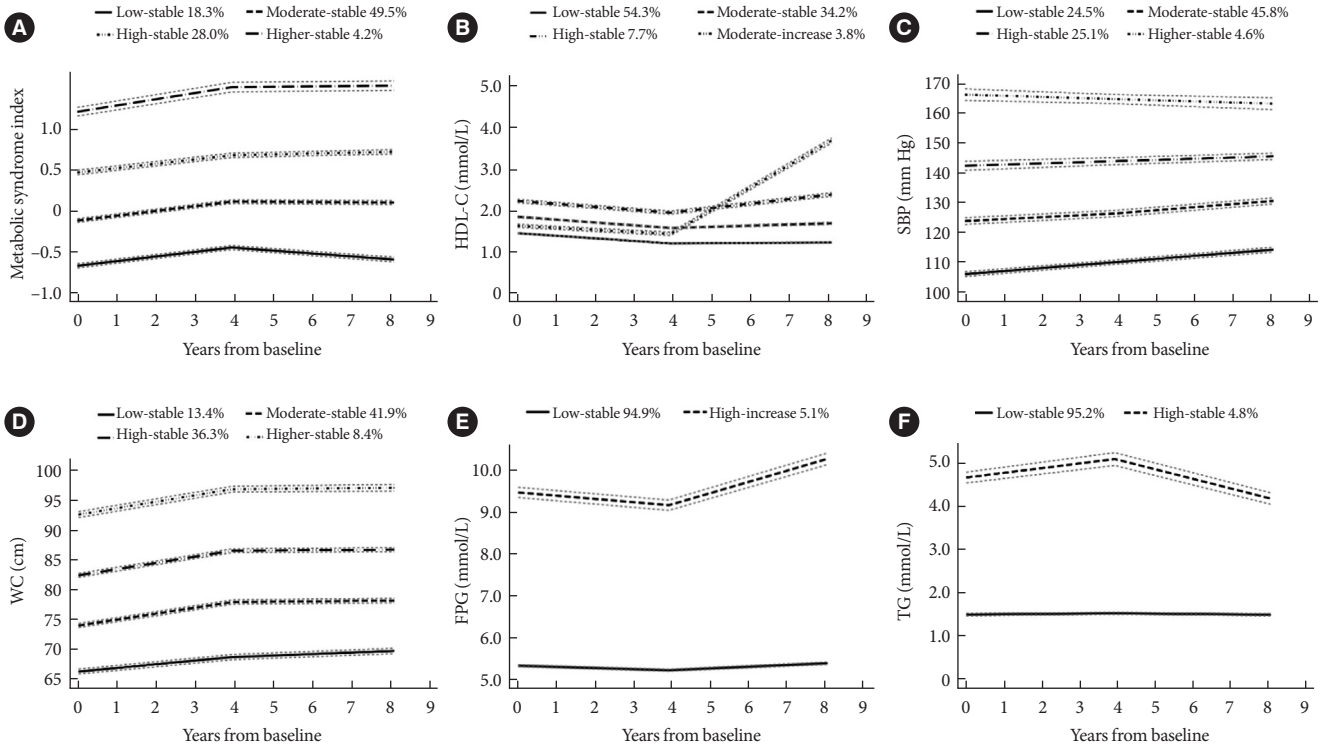

Fig. 1. Trajectory groups of metabolic syndrome (MetS) index and its components over 12-year follow-up. Values are means and 95% confidence interval (CI) for MetS index and its components. The components of MetS index included high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), waist circumference (WC), fasting plasma glucose (FPG), and triglyceride (TG). Four trajectory groups for (A) MetS index, (B) HDL-C, (C) SBP, and (D) WC, and two trajectory groups for (E) FPG and (F) TG were identified using group-based trajectory model, with standard of lower Bayesian information criterion and average posterior probability >0.7.

Table 1. Baseline characteristics of participants by metabolic syndrome index trajectory groups, Guangzhou Biobank Cohort Study, 2003 to 2008

Characteristic	MetS index trajectory groups				*P* value
	Low-stable	Moderate-stable	High-stable	Higher-stable	
Number	1,420 (18.3)	3,854 (49.5)	2,173 (28.0)	328 (4.2)	
Age, yr	57.2±5.7	59.3±6.0	60.7±6.1	60.0±5.9	<0.001
Sex					
Women	1,219 (85.9)	2,958 (76.7)	1,408 (64.8)	187 (57.0)	<0.001
Men	201 (14.2)	896 (23.3)	765 (35.2)	141 (43.0)	
Education					
Junior middle or below	728 (51.3)	2,319 (60.2)	1,398 (63.3)	205 (62.5)	<0.001
Senior middle or above	692 (48.7)	1,534 (39.8)	775 (36.7)	123 (37.5)	
Occupation					
Manual	776 (55.3)	2,180 (56.9)	1,221 (56.7)	185 (56.6)	0.050
Non-manual	359 (25.5)	1,005 (26.3)	611 (28.3)	90 (27.5)	
Others	269 (19.2)	643 (16.8)	323 (15.0)	52 (15.9)	
Marital status					
Married	808 (85.3)	2,279 (86.5)	1,310 (86.9)	187 (87.0)	0.712
Others	139 (14.7)	356 (13.5)	197 (13.1)	28 (13.0)	
Smoking status					
Never	1,283 (90.5)	3,303 (85.8)	1,725 (79.4)	246 (75.2)	<0.001
Ever	135 (9.5)	545 (14.2)	447 (10.6)	81 (24.8)	
Drinking status					
Never	969 (68.7)	2,681 (69.9)	1,458 (67.3)	197 (60.6)	<0.002
Ever	442 (31.3)	1,152 (30.1)	707 (32.7)	128 (39.4)	
Family income, CNY/yr[a]					
<30,000	472 (38.9)	1,292 (41.1)	717 (41.7)	124 (4613)	0.138
≥30,000	742 (61.1)	1,852 (58.9)	1,002 (58.3)	145 (53.9)	
Physical activity					
Inactive	134 (9.4)	312 (8.1)	181 (8.3)	26 (7.9)	0.027
Minimally active	495 (34.9)	1,443 (37.4)	854 (39.3)	144 (43.9)	
Active	791 (55.7)	2,099 (54.5)	1,238 (52.4)	158 (48.2)	
BMI, kg/m^2	20.9±2.5	23.3±2.6	25.6±2.8	26.6±3.2	<0.001
Self-rated health, poor/very poor	253 (18.3)	522 (13.9)	310 (14.6)	65 (20.1)	0.001
Cardiovascular disease, yes	338 (23.8)	1,357 (35.2)	1,110 (51.2)	195 (59.5)	<0.001
Hyperlipidemia, yes	101 (7.1)	346 (9.0)	356 (16.4)	77 (23.5)	<0.001
Diabetes, yes	13 (1.0)	101 (2.6)	251 (11.6)	88 (26.8)	<0.001
Hypertension, yes	97 (6.8)	749 (19.4)	844 (38.9)	152 (46.3)	<0.001
Drug for hypertension, glucose or lipids, yes	127 (9.6)	817 (22.6)	937 (45.1)	188 (59.1)	<0.001
DWRT score	6.5±1.5	6.2±1.5	6.1±1.5	6.0±1.5	<0.001
IWRT score	18.1±3.4	17.5±3.5	17.1±3.6	17.0±3.7	<0.001
MMSE score	28.6±1.3	28.5±1.3	28.5±1.3	28.4±1.4	0.134

Values are presented as number (%) or mean±standard deviation.
MetS, metabolic syndrome; CNY, Chinese yuan; BMI, body mass index; DWRT, delayed 10-word recall test; IWRT, immediate 10-word recall test; MMSE, mini-mental state examination.
[a]US$1=6.95 CNY.

found between the MetS index trajectory groups and occupation, marital status, family income or baseline MMSE scores (P=0.050 to 0.712).

In Table 2, model 2, after adjusting for potential confounders, higher MetS index was associated with decreasing annual change rates (decrease) in DWRT, IWRT, and MMSE scores, and the associations with decreases in DWRT and MMSE scores were statistically significant (adjusted β=–0.014 score/year [95% CI, –0.025 to –0.003] and –0.026 score/year [95% CI, –0.042 to –0.010], respectively), while with a decrease in IWRT scores was non-significant (–0.015 score/year [95% CI, –0.039 to 0.008]). MetS index trajectory groups were identified, including low-stable, moderate-stable, high-stable, and higher-stable groups (Fig. 1). Compared to the low-stable MetS index group, the higher-stable group showed significant decreases in DWRT and IWRT scores (–0.048 score/year [95% CI, –0.088 to –0.008] and –0.093 score/year [95% CI, –0.180 to –0.006], respectively). Similar patterns were also found in both moderate and high-stable MetS index groups. No associations were found of the MetS index trajectory groups with changes in MMSE scores (P=0.081 to 0.743). Regarding the five dimensions of MMSE, the MetS index was significantly associated with decreases in attention and calculation, and recall scores (–0.014 score/year [95% CI, –0.022 to –0.005] and –0.021 score/year [95% CI, –0.029 to –0.012], respectively). Conversely, it was associated with a slight increase in registration scores (0.004 score/year [95% CI, 0.002 to 0.006]). Furthermore, compared to the low-stable MetS index group, the high-stable group showed statistically associated decreases in attention and calculation, and recall scores (–0.016 score/year [95% CI, –0.036 to –0.001] and –0.024 score/year [95% CI, –0.041 to –0.007], respectively). However, no associations of the MetS index and its trajectory groups with changes in orientation and language scores were found (P=0.066 to 0.449).

Moreover, the trajectory groups of the MetS index components including HDL-C, SBP, WC, FPG, and TG are shown in Fig. 1, and the associations with annual change rates in DWRT, IWRT, MMSE, and its dimensions were also explored as shown in Fig. 2. Compared to the low-stable status group, the high-stable SBP group and the high-increase FPG group were associated with significant decreasing annual change rates (decrease) in both DWRT and IWRT scores (–0.055 score/year [95% CI, –0.090 to –0.021] and –0.050 score/year [95% CI, –0.082 to –0.019] for DWRT, and –0.077 score/year [95% CI, –0.152 to –0.003] and –0.084 score/year [95% CI, –0.152 to –0.015] for IWRT, respectively). Conversely, the moderate-increase HDL-C group was associated with significant increases in DWRT and IWRT scores (0.087 score/year [95% CI, 0.052 to 0.123] and 0.110 score/year [95% CI, 0.033 to 0.187], respectively). HDL-C was positively associated with an increase in MMSE scores (0.052 score/year [95% CI, 0.035 to 0.070]), while WC showed a negative association (–0.002 score/year [95% CI, –0.003 to –0.001]). Such associations were also found in the moderate-increase HDL-C and higher-stable WC group, relative to their respective stable groups (Fig. 2).

Regarding the five dimensions of MMSE, the positive associations of HDL-C with increasing annual change rates (increase) in attention and calculation, and recall scores were found (0.020 score/year [95% CI, 0.011 to 0.029] and 0.033 score/year [95% CI, 0.024 to 0.042], respectively) (Fig. 2). Conversely, an association of WC with decreases in attention and calculation, and recall scores was found (both –0.002 score/year [95% CI, –0.003 to –0.001]). Compared to the low-stable status group, the moderate-increase HDL-C group was significantly associated with increases in attention and calculation, and recall scores (0.052 score/year [95% CI, 0.028 to 0.077] and 0.050 score/year [95% CI, 0.026 to 0.074], respectively), while the higher-stable WC group was associated with a decrease in recall scores (–0.032 score/year [95% CI, –0.057 to –0.007]). The high-increase FPG group was associated with a decrease in registration scores (–0.007 score/year [95% CI, –0.014 to –0.003]). No associations of SBP and TG with the five dimensions of MMSE were found (Fig. 2).

In the modification analysis, as shown in Supplementary Fig. 1, the associations of the MetS index with annual change rates in DWRT and IWRT scores did not vary by sex, age, education nor family income (P for interactions from 0.17 to 0.73). However, the association with MMSE scores varied by family income (P for interaction=0.03), with a more pronounced decreasing annual change rates in MMSE scores associated with a higher MetS index being observed in the low family income group (–0.050 score/year [95% CI, –0.078 to –0.022]). Additionally, a significant modification effect of family income was observed in the attention and calculation dimension of the MMSE, indicating a more pronounced association in the low family income group (P for interaction=0.02).

GWAS and MR analysis results

A total of 2,705 participants had baseline data on MetS and genotyping. In Fig. 3 and Supplementary Table 2, the Manhattan plot identified 46 SNPs achieving genome-wide significance

Table 2. Longitudinal association of MetS index and its trajectory groups with annual change rates in memory and cognitive function scores based on linear mixed-effect model over 12-year follow-up

Variable	No. (%)	Crude β (95% CI)	*P* value	Model 1[a]	*P* value	Model 2[b]	*P* value
DWRT							
MetS index×time[c,d]	7,775	−0.013 (−0.022 to −0.004)[g]	0.003	−0.015 (−0.026 to −0.004)[g]	0.006	−0.014 (−0.025 to −0.003)[f]	0.010
MetS index trajectory groups×time[d]							
Low-stable	1,420 (18.3)	0.000		0.000		0.000	
Moderate-stable	3,854 (49.5)	−0.023 (−0.038 to −0.008)[g]	0.003	−0.028 (−0.048 to −0.007)[g]	0.007	−0.028 (−0.048 to −0.007)[g]	0.007
High-stable	2,173 (28.0)	−0.033 (−0.049 to −0.016)[h]	<0.001	−0.038 (−0.060 to −0.015)[g]	0.001	−0.037 (−0.059 to −0.015)[g]	0.001
Higher-stable	328 (4.2)	−0.053 (−0.083 to −0.022)[g]	0.001	−0.048 (−0.088 to −0.008)[f]	0.019	−0.048 (−0.088 to −0.008)[f]	0.019
IWRT							
MetS index×time[c,d]	7,775	−0.009 (−0.028 to 0.009)	0.320	−0.016 (−0.040 to 0.007)	0.176	−0.015 (−0.039 to 0.008)	0.210
MetS index trajectory groups×time[d]							
Low-stable	1,420 (18.3)	0.000		0.000		0.000	
Moderate-stable	3,854 (49.5)	−0.052 (−0.084 to −0.020)[g]	0.002	−0.077 (−0.121 to −0.033)[g]	0.001	−0.076 (−0.120 to −0.032)[g]	0.001
High-stable	2,173 (28.0)	−0.072 (−0.107 to −0.037)[h]	<0.001	−0.082 (−0.130 to −0.035)[g]	0.001	−0.082 (−0.129 to −0.034)[g]	0.001
Higher-stable	328 (4.2)	−0.093 (−0.156 to −0.030)[g]	0.004	−0.091 (−0.178 to −0.005)[f]	0.039	−0.093 (−0.180 to −0.006)[f]	0.039
MMSE							
MetS index×time[c,d]	3,251	−0.028 (−0.043 to −0.013)[h]	<0.001	−0.026 (−0.041 to −0.010)[g]	0.001	−0.026 (−0.042 to −0.010)[g]	0.001
MetS index trajectory groups×time[d]							
Low-stable	700 (22.7)	0.000		0.000		0.000	
Moderate-stable	1,480 (48.0)	−0.019 (−0 to044 to 0.006)	0.138	−0.014 (−0.041 to 0.014)	0.286	−0.014 (−0.041 to 0.014)	0.286
High-stable	769 (24.9)	−0.026 (−0.055 to 0.003)	0.074	−0.027 (−0.058 to 0.004)	0.078	−0.027 (−0.057 to 0.005)	0.081
Higher-stable	137 (4.4)	0.003 (−0.049 to 0.055)	0.920	0.009 (−0.046 to 0.064)	0.739	0.009 (−0.046 to 0.064)	0.743
Orientation[e]							
MetS index×time[c,d]	3,251	0.004 (−0.001 to 0.008)[f]	0.123	0.004 (−0.001 to 0.008)	0.155	0.004 (−0.001 to 0.008)	0.140
MetS index trajectory groups×time[d]							
Low-stable	700 (22.7)	0.000		0.000		0.000	
Moderate-stable	1,480 (48.0)	0.006 (−0.002 to 0.014)	0.138	0.007 (−0.001 to 0.015)	0.086	0.007 (−0.001 to 0.015)	0.085
High-stable	769 (24.9)	0.006 (−0.004 to 0.015)	0.242	0.006 (−0.003 to 0.015)	0.201	0.006 (−0.003 to 0.015)	0.198
Higher-stable	137 (4.4)	0.011 (−0.006 to 0.027)	0.205	0.009 (−0.007 to 0.025)	0.259	0.009 (−0.007 to 0.025)	0.262
Registration[e]							
MetS index×time[c,d]	3,251	0.004 (0.002 to 0.007)[h]	<0.001	0.004 (0.002 to 0.006)[g]	0.001	0.004 (0.002 to 0.006)[g]	0.001
MetS index trajectory groups×time[d]							

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Table 2. Continued

Variable	No. (%)	Crude β (95% CI)	*P* value	Model 1[a]	*P* value	Model 2[b]	*P* value
Low-stable	700 (22.7)	0.000		0.000		0.000	
Moderate-stable	1,480 (48.0)	0.001 (−0.002 to 0.005)	0.503	0.002 (−0.002 to 0.006)	0.245	0.002 (−0.001 to 0.006)	0.245
High-stable	769 (24.9)	0.001 (−0.002 to 0.006)	0.302	0.003 (−0.001 to 0.007)	0.189	0.003 (−0.001 to 0.007)	0.156
Higher-stable	137 (4.4)	0.002 (−0.006 to 0.009)	0.630	0.001 (−0.007 to 0.008)	0.902	0.001 (−0.007 to 0.008)	0.899
Attention and calculation[e]							
MetS index×time[c,d]	3,251	−0.017 (−0.025 to −0.008)[h]	<0.001	−0.014 (−0.022 to −0.005)[g]	0.001	−0.014 (−0.022 to −0.005)[g]	0.001
MetS index trajectory groups×time[d]							
Low-stable	700 (22.7)	0.000		0.000		0.000	
Moderate-stable	1,480 (48.0)	−0.017 (−0.031 to −0.004)[f]	0.014	−0.015 (−0.030 to 0.001)	0.061	−0.015 (−0.030 to 0.001)	0.060
High-stable	769 (24.9)	−0.020 (−0.036 to −0.002)[f]	0.013	−0.018 (−0.036 to −0.001)[f]	0.037	−0.016 (−0.036 to −0.001)[f]	0.036
Higher-stable	137 (4.4)	−0.008 (−0.036 to 0.020)	0.580	−0.002 (−0.033 to 0.029)	0.862	−0.002 (−0.033 to 0.029)	0.860
Recall[e]							
MetS index×time[c,d]	3,251	−0.021 (−0.030 to −0.013)[h]	<0.001	−0.020 (−0.029 to −0.012)[h]	<0.001	−0.021 (−0.029 to −0.012)[h]	<0.001
MetS index trajectory groups×time[d]							
Low-stable	700 (22.7)	0.000		0.000		0.000	
Moderate-stable	1,480 (48.0)	−0.016 (−0.030 to −0.001)[f]	0.033	−0.013 (−0.028 to 0.002)	0.069	−0.013 (−0.028 to 0.001)	0.070
High-stable	769 (24.9)	−0.021 (−0.038 to −0.005)[f]	0.012	−0.024 (−0.041 to −0.007)[g]	0.006	−0.024 (−0.041 to −0.007)[g]	0.006
Higher-stable	137 (4.4)	−0.004 (−0.033 to 0.026)	0.816	−0.001 (−0.032 to 0.029)	0.927	−0.002 (−0.032 to 0.028)	0.926
Language[e]							
MetS index×time[c,d]	3,251	0.003 (−0.001 to 0.008)	0.126	0.003 (−0.002 to 0.007)	0.227	0.002 (−0.002 to 0.007)	0.222
MetS index trajectory groups×time[d]							
Low-stable	700 (22.7)	0.000		0.000		0.000	
Moderate-stable	1,480 (48.0)	0.008 (0.001 to 0.016)[f]	0.026	0.006 (−0.001 to 0.013)	0.072	0.006 (−0.001 to 0.013)	0.071
High-stable	769 (24.9)	0.008 (−0.001 to 0.017)	0.053	0.008 (−0.001 to 0.016)	0.068	0.008 (−0.001 to 0.016)	0.066
Higher-stable	137 (4.4)	0.005 (−0.010 to 0.020)	0.511	0.005 (−0.010 to 0.019)	0.446	0.005 (−0.010 to 0.019)	0.449

MetS, metabolic syndrome; CI, confidence interval; DWRT, delayed 10-word recall test; IWRT, immediate 10-word recall test; MMSE, mini-mental state examination.
[a]Model 1: adjusted for sex, age, baseline memory or cognitive function scores, body mass index, education, occupation, marital status, smoking status, drinking status, family income, physical activity, and self-rated health, [b]Model 2: additionally adjusted for self-reported cardiovascular disease, hypertension, diabetes, hyperlipidemia, and drug history, [c]The construction of MetS index based on fasting plasma glucose, triglycerides, systolic pressure, reversed high-density lipoprotein cholesterol, and waist circumference, [d]β coefficient and its 95% CI were reported as score per year, [e]MMSE consists of five dimensions: orientation, registration, attention and calculation, recall, and language, [f]$P<0.05$, [g]$P<0.01$, [h]$P<0.001$.

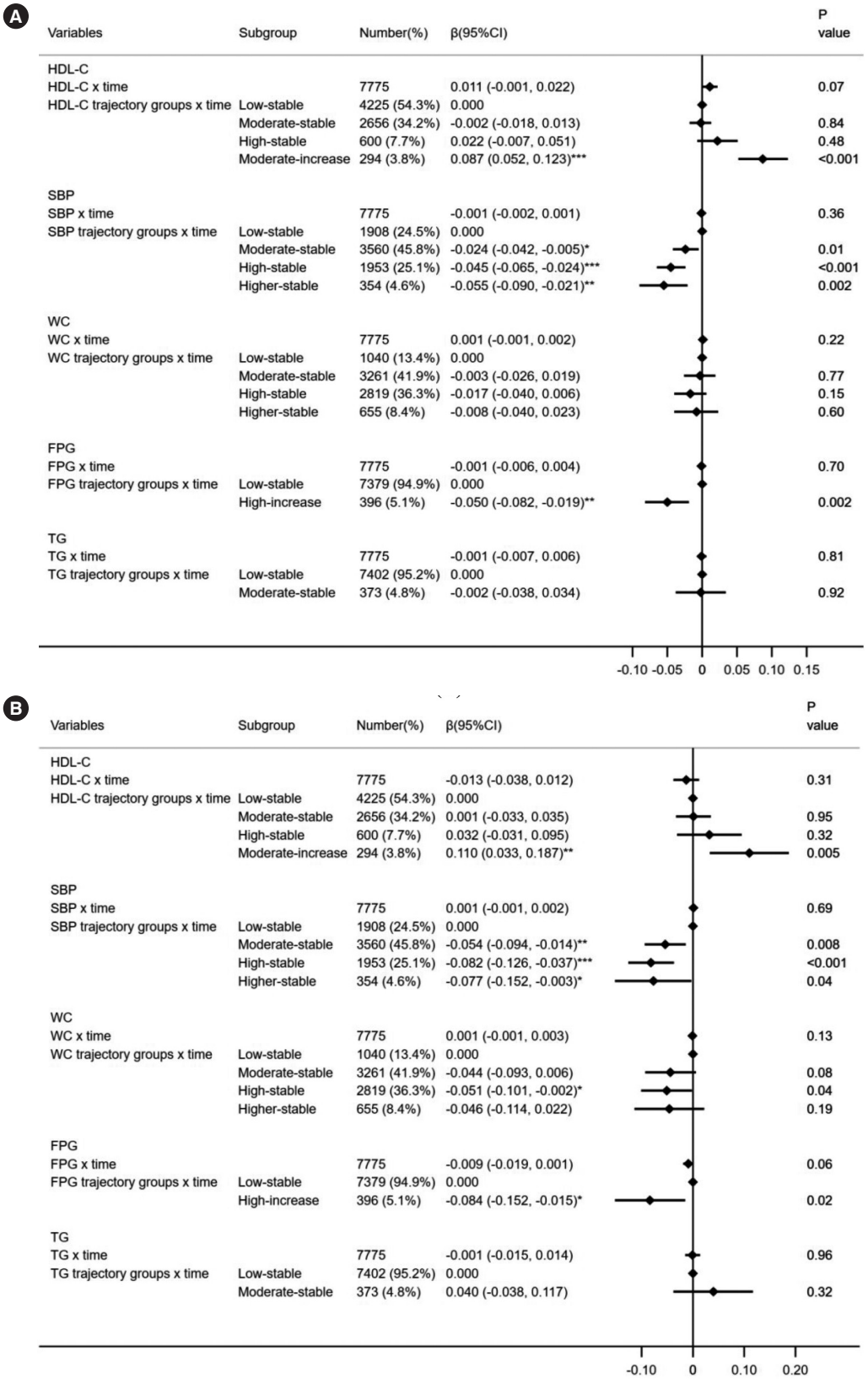

Fig. 2. Continued.

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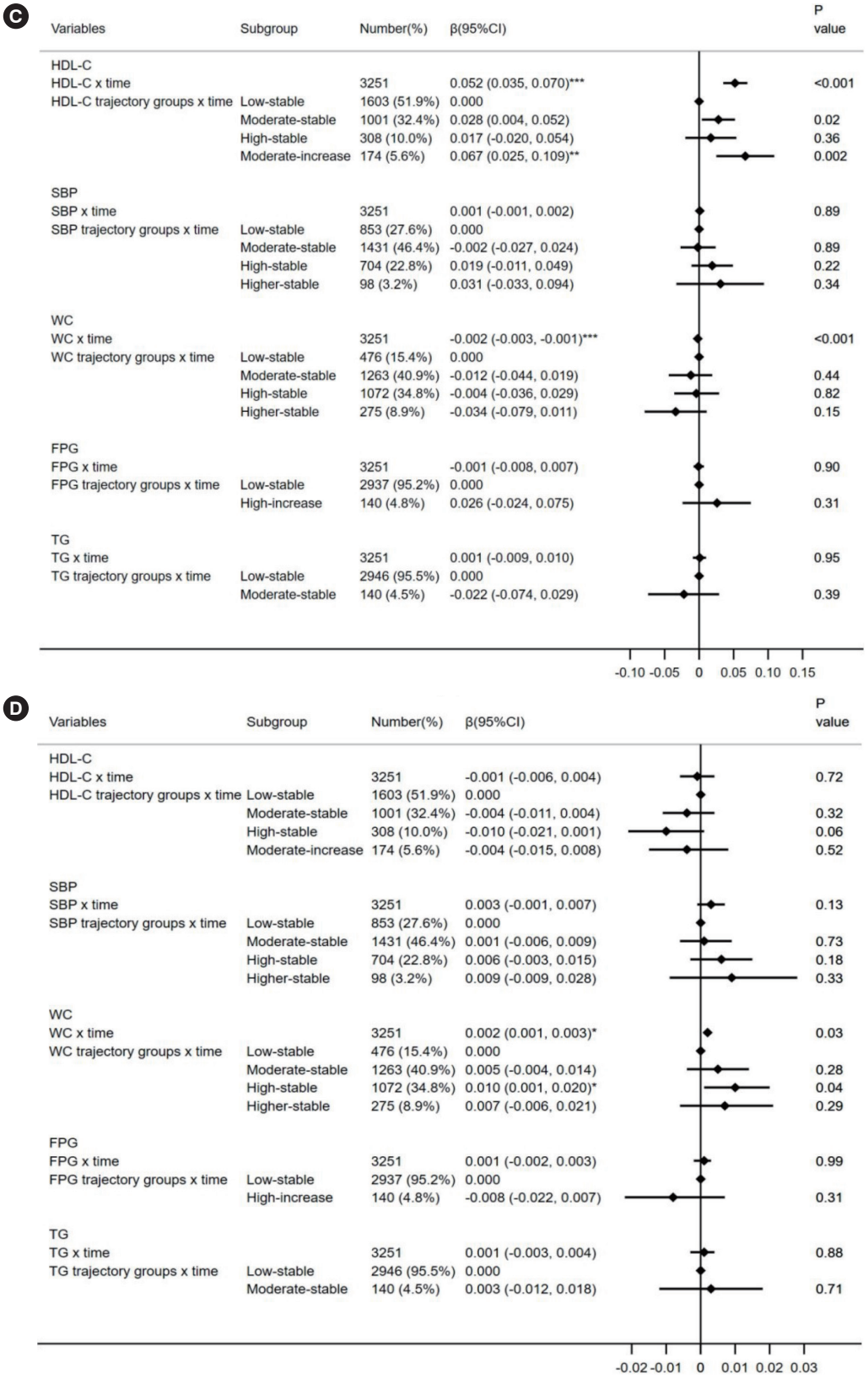

Fig. 2. Continued.

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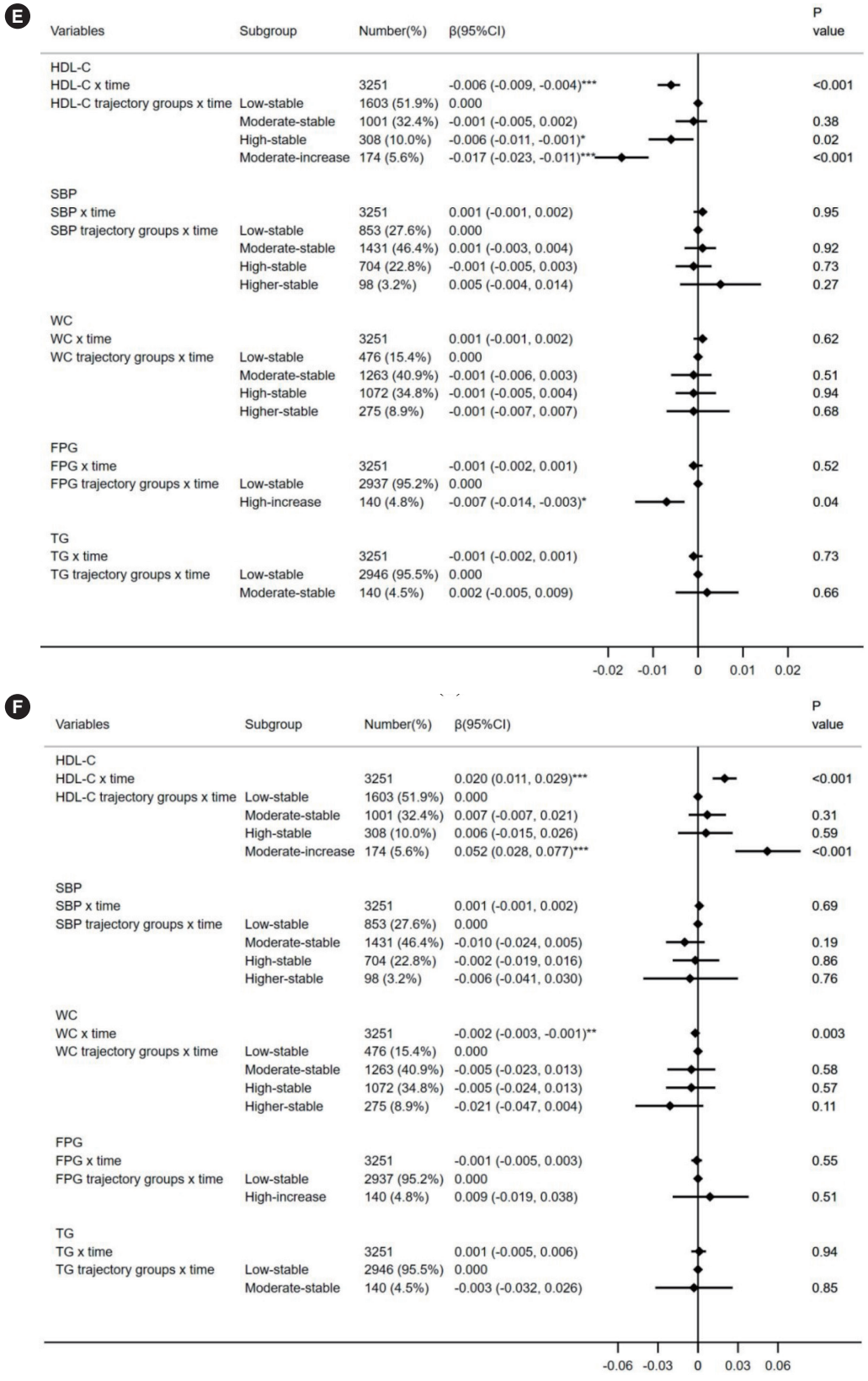

Fig. 2. Continued.

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G

Variables	Subgroup	Number(%)	β(95%CI)	P value
HDL-C				
HDL-C x time		3251	0.033 (0.024, 0.042)***	<0.001
HDL-C trajectory groups x time	Low-stable	1603 (51.9%)	0.000	
	Moderate-stable	1001 (32.4%)	0.024 (0.010, 0.037)**	0.001
	High-stable	308 (10.0%)	0.030 (0.010, 0.050)**	0.004
	Moderate-increase	174 (5.6%)	0.050 (0.026, 0.074)***	<0.001
SBP				
SBP x time		3251	-0.001 (-0.002, 0.001)	0.08
SBP trajectory groups x time	Low-stable	853 (27.6%)	0.000	
	Moderate-stable	1431 (46.4%)	0.001 (-0.014, 0.015)	0.96
	High-stable	704 (22.8%)	0.011 (-0.005, 0.028)	0.19
	Higher-stable	98 (3.2%)	0.007 (-0.028, 0.042)	0.69
WC				
WC x time		3251	-0.002 (-0.003, -0.001)**	0.003
WC trajectory groups x time	Low-stable	476 (15.4%)	0.000	
	Moderate-stable	1263 (40.9%)	-0.014 (-0.032, 0.003)	0.12
	High-stable	1072 (34.8%)	-0.015 (-0.032, 0.003)	0.11
	Higher-stable	275 (8.9%)	-0.032 (-0.057, -0.007)*	0.01
FPG				
FPG x time		3251	-0.001 (-0.004, 0.003)	0.94
FPG trajectory groups x time	Low-stable	2937 (95.2%)	0.000	
	High-increase	140 (4.8%)	0.023 (-0.004, 0.050)	0.10
TG				
TG x time		3251	-0.001 (-0.006, 0.004)	0.77
TG trajectory groups x time	Low-stable	2946 (95.5%)	0.000	
	Moderate-stable	140 (4.5%)	-0.016 (-0.044, 0.013)	0.28

H

Variables	Subgroup	Number(%)	β(95%CI)	P value
HDL-C				
HDL-C x time		3251	0.003 (-0.003, 0.007)	0.29
HDL-C trajectory groups x time	Low-stable	1603 (51.9%)	0.000	
	Moderate-stable	1001 (32.4%)	0.001 (-0.005, 0.007)	0.77
	High-stable	308 (10.0%)	-0.003 (-0.013, 0.006)	0.50
	Moderate-increase	174 (5.6%)	-0.013 (-0.024, -0.002)*	0.02
SBP				
SBP x time		3251	0.001 (-0.001, 0.002)	0.73
SBP trajectory groups x time	Low-stable	853 (27.6%)	0.000	
	Moderate-stable	1431 (46.4%)	0.006 (-0.001, 0.013)	0.07
	High-stable	704 (22.8%)	0.004 (-0.004, 0.012)	0.33
	Higher-stable	98 (3.2%)	0.015 (-0.001, 0.032)	0.07
WC				
WC x time		3251	0.001 (-0.001, 0.002)	0.74
WC trajectory groups x time	Low-stable	476 (15.4%)	0.000	
	Moderate-stable	1263 (40.9%)	0.004 (-0.004, 0.012)	0.33
	High-stable	1072 (34.8%)	0.007 (-0.001, 0.016)	0.09
	Higher-stable	275 (8.9%)	0.014 (0.002, 0.026)*	0.02
FPG				
FPG x time		3251	0.002 (-0.001, 0.004)	0.12
FPG trajectory groups x time	Low-stable	2937 (95.2%)	0.000	
	High-increase	140 (4.8%)	0.009 (-0.004, 0.022)	0.16
TG				
TG x time		3251	0.001 (-0.002, 0.003)	0.89
TG trajectory groups x time	Low-stable	2946 (95.5%)	0.000	
	Moderate-stable	140 (4.5%)	-0.008 (-0.022, 0.005)	0.24

Fig. 2. Continued.

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Fig. 2. (Continued) Forest plots for the longitudinal association of the components of metabolic syndrome (MetS) index and their trajectory groups with annual change rates in (A) delayed 10-word recall test (DWRT), (B) immediate 10-word recall test (IWRT) and (C) mini-mental state examination (MMSE), (D) orientation, (E) registration, (F) attention and calculation, (G) recall, and (H) language scores based on linear-mixed effect model over 12-year follow-up. β and 95% confidence interval (CI) were adjusted for sex, age, baseline memory or cognitive function scores, body mass index, education, occupation, marital status, smoking status, drinking status, family income, physical activity, self-rated health, self-reported cardiovascular disease, hypertension, diabetes, hyperlipidemia and drug history. The components of MetS index included high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), waist circumference (WC), fasting plasma glucose (FPG), and triglyceride (TG). MMSE consists of five dimensions: orientation, registration, attention and calculation, recall, and language.

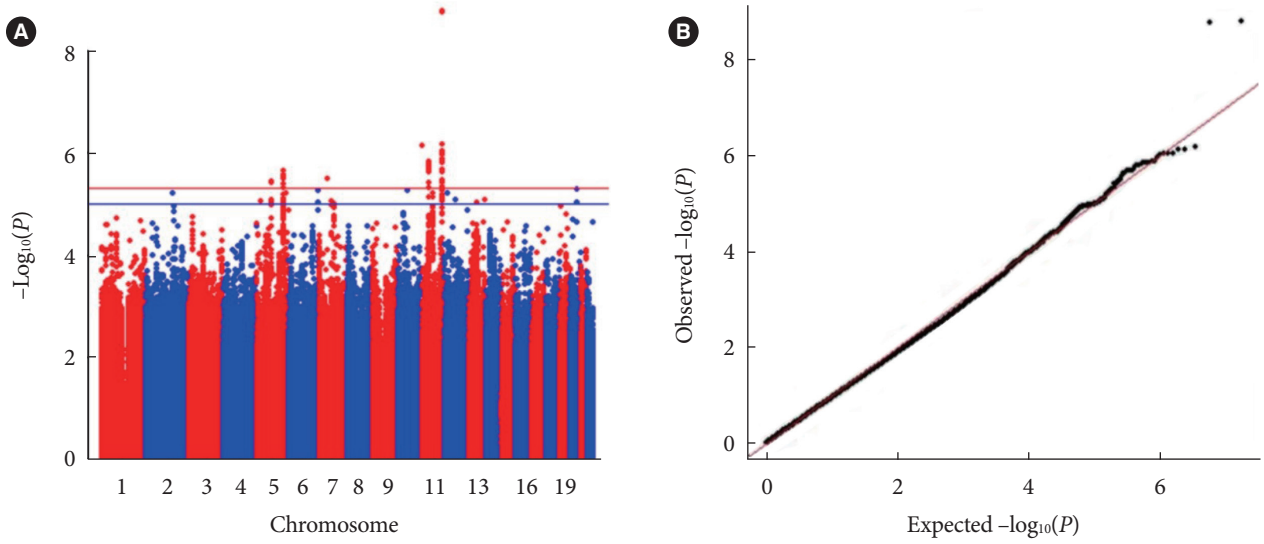

Fig. 3. (A) Manhattan plot and (B) quantile-quantile (Q-Q) plot for metabolic syndrome in the genome-wide association study involving 2,705 participants of the Guangzhou Biobank Cohort Study (2003 to 2008). The x-axis is chromosomal position, and the y-axis is the significance on a $-\log_{10}$ scale. The red line shows the genome-wide significance level (5×10^{-6}).

Table 3. The selected two related SNPs from the GWAS of MetS involving 2,705 participants of the Guangzhou Biobank Cohort Study, 2003 to 2008

SNP	Nearest gene	Chr	Position	Risk/other allele	MAF, %	β	R^2	*P* value
Previous								
rs662799[a]	APOA5	11	116663707	G/A	28	0.4025	0.0467	1.67E-09
New								
rs1989154[a]	HTR4	5	147848890	C/T	20	0.3837	0.0291	2.28E-06

$R^2=2\times(1-\mathrm{MAF})\times\mathrm{MAF}\times\frac{\beta}{\mathrm{SD}}$; $\mathrm{SD}=\mathrm{SE}\times\sqrt{n}$.

SNP, single nucleotide polymorphism; GWAS, genome-wide association study; MetS, metabolic syndrome; Chr, chromosome; MAF, minor allele frequency; APOA5, apolipoprotein A5; HTR4, 5-hydroxytryptamine receptor 4.

[a]After assessed by linkage disequilibrium ($r^2\geq0.1$) and Hardy-Weinberg equilibrium, the genetically estimated MetS score = rs662799×0.4025+rs1989154×0.3837.

associated with MetS ($P<5\times10^{-6}$). For example, rs662799 in chromosome 11, which tags the apolipoprotein A5 (APOA5) allele, exhibited the strongest effect size ($P=1.67\times10^{-9}$). After excluding SNPs that deviated from the Hardy-Weinberg equilibrium and showed high LD ($r^2\geq0.1$), a weighted genetic score was constructed using two SNPs, with their beta-coefficient derived from the GWAS (Table 3). Of them, rs662799 has been previously reported, while rs1989154, tagging the 5-hydroxytryptamine receptor 4 (HTR4) gene, represented a novel locus for MetS. When using the weighted genetic score as IV in the

one-sample MR analysis, the results indicated a non-significant causal association between MetS and decrease in DWRT, IWRT nor MMSE scores (P=0.29 to 0.98) (Supplementary Table 3).

DISCUSSION

Principal findings

To date, our study is the first to establish the longitudinal association of changes in MetS, expressed as an index, with cognitive decline in 7,775 older Chinese adults over a 12-year follow-up. We found that greater MetS index was significantly associated with declines in memory and cognitive function, especially in delayed memory recall. This association was also evident in the higher-stable MetS index group compared to the low-stable MetS index group. Additionally, our results showed that in the components of MetS index, HDL-C was positively associated with annual change rates in memory function, while SBP and FPG were negatively associated. Moreover, HDL-C showed a positive association, whereas WC was negatively associated with changes in cognitive function, including the dimensions of attention, calculation and recall. The association of the MetS index on cognitive decline was predominantly observed in participants with low family income (as an indicator of social deprivation), with no such association noted in those with high family income. The GWAS of MetS (case-control) identified some significant SNPs in the Chinese population. The one-sample MR results showed the non-significant causal association between MetS and memory and cognitive decline. Our results suggest the importance of managing MetS and its components in older adults, potentially aiding in delaying or preventing cognitive impairment, especially in delayed memory recall.

Comparison with previous studies

Our results of a significant association of MetS with memory and cognitive decline were in line with some [31-33] but not all [34,35] previous studies, which all used dichotomous classification of MetS. For example, a longitudinal study of 4,150 British participants with an average age of 60 years, measured MetS at three different time points and found that participants with persistent MetS showed poorer cognitive performance than their healthy participants over a 10-year follow-up [33], though cognitive function was only assessed at the end of follow-up. Another cohort study on 4,106,590 Korean participants aged over 40 years and with an average follow-up of 4.9 years, indicated that those with persistent or developing MetS had a higher risk of dementia compared to healthy participants [31]. A similar association was reported in another longitudinal study involving 1,492,776 Korean participants with an average follow-up of 5.2 years [32]. Notably, these studies excluded participants previously diagnosed with dementia, but those with pre-clinical symptoms (i.e., memory loss) might not be identified and subsequently lead to over-estimated results. Conversely, one study based on 5,693 Taiwan participants with a mean age of 63 years and measuring MetS at two different time points, found a non-significant association between developing MetS and dementia risk over a 10-year follow-up [34]. Similarly, another cohort study based on 3,458 Taiwan participants aged over 40 years, also measuring MetS at two different time points, reported a non-significant association between persistent MetS and cognitive decline [35]. The lack of significance in these studies may be attributed to the use of dichotomous classification of MetS, which could reduce the statistical power. Additionally, the heterogeneity in the reference groups could explain the inconsistent results across studies. Therefore, the current dichotomous classification of MetS may not optimally explore the risk of cognitive decline. Previous studies showed that the MetS index was an accurate predictor of the 10-year incidence of cardiovascular disease, suggesting that this index, when used as a standardized continuous variable, was more sensitive in detecting the association with cognitive function [10,36]. Hence, our study provides complementary evidence suggesting that MetS should be considered as a continuum rather than dichotomy.

Moreover, most previous studies describing the association of MetS and its components with cognitive function did not specifically examine the dimensions of cognitive function [5,34]. For example, a prospective study of 5,693 participants in Taiwan with a 10-year follow-up indicated that, compared to healthy participants, those with lower HDL-C levels and higher blood pressure and WC levels at baseline had a higher risk of dementia [34]. Another prospective study of 1,519 participants in Singapore with a 6-year follow-up also showed that higher WC and lower HDL-C levels at baseline showed a positive association with the risk of mild cognitive impairment [5]. Given that both abnormal WC and FPG levels are indicative of insulin resistance, our results are in corroborate with these previous studies. Regarding the dimension of cognitive function, our results suggest that MetS and its components mainly

affect attention, calculation, and recall abilities, aligning with previous studies. A systematic review of 19 cohort studies indicated that MetS-related decline in attention, calculation and recall abilities was evident prior to the onset of dementia [37]. However, the Taiwan study reported non-significant associations of baseline MetS and its components with these cognitive dimensions when compared to healthy participants [34]. Another cohort study of 599 Dutch participants over a 5-year follow-up indicated a positive association of baseline MetS status with increasing annual change rates in attention and memory function [38]. Notably, as the average age of participants in this Dutch study was 85 years, survival bias may be a concern.

In our GWAS, we identified significant genetic variants associated with MetS located in the genes of APOA5, zinc finger protein 259 (ZNF259), BUD13 homolog (BUD13) and HTR4. For example, rs662799 in the APOA5 gene, rs6589566 in the ZNF259 gene, and rs10790162 in the BUD13 gene are strongly associated with MetS in our study, aligning with findings from previous studies [16,39,40]. The genetic variants in the APOA5 gene on chromosome 11 are known to influence lipid metabolism [41]. Both the ZNF259 and BUD13 genes, situated in the APOA5 gene cluster on chromosome 11q23.3, have functions similar to the APOA5 gene, affecting lipid metabolism [42]. The role of the APOA5 gene cluster involves either intracellular inhibition of the very low-density lipoprotein (VLDL) assembly or activation of lipoprotein lipase, enhancing lipolysis and VLDL clearance [41]. Therefore, variants in the APOA5 gene could contribute to or exacerbate the dyslipidemia components of MetS, leading to decreased HDL-C levels and increased TG levels.

Moreover, our study is the first to report that the HTR4 gene variant rs1989154 is significantly associated with MetS in Chinese participants. The HTR4 gene at chromosome 5 has been associated with obesity [43]. Previous studies showed that 5-hydroxytryptamine, regulated by the HTR4 gene, was a monoamine neurotransmitter acting as a satiety-generating signal in the brain tissue which regulated food intake in both experimental models and humans [43,44]. Variants in the HTR4 gene might increase the propensity for eating, thereby contributing to the obesity components of MetS. However, due to resource constraints, replication of this genetic variant could not be tested in another sample. Future studies are needed to replicate this locus in other populations.

Our results showed that the association of an elevated MetS index with cognitive decline was more pronounced in participants with low family income, indicating that individuals who were more socially deprived might suffer more from the metabolic abnormality. A cross-sectional study of 5,200 United States participants with high socioeconomic position, as expressed by high educational attainment (median, 16.0 years; interquartile range, 16.0 to 18.0 years of education attained), showed a non-significant association between MetS and cognitive impairment [45]. The authors further examined differences in the MetS-cognitive impairment association by levels of sociodemographic (age, sex, education) and clinical factors but did not observe significant variation [45]. A possible explanation is that individuals who are more socially deprived (i.e., low family income or low socioeconomic position) might increase vulnerability to disease through direct physiological process and unhealthy behaviors [46]. Additionally, limited resources also play a role. Participants with low family income are less likely to have adequate healthcare utilization or access to other essential services. These factors may collectively exacerbate the impact of MetS and the related burdens.

Mechanism

The mechanism underlying the association between MetS and cognitive decline may be attributed to the multifactorial pathogenesis of its components. For example, dyslipidemia can lead to dysfunction of the cellular lipid membranes. This dysfunction may augment the enzymatic activity of beta-site amyloid precursor protein cleavage enzyme-1 (BACE-1) and gamma-secretase, thereby accelerating the cleavage of amyloid precursor protein (APP). Consequently, this process could result in increased production of β-amyloid plaques [47]. Hypertension may cause alterations in cerebral vessels, leading to endothelial dysfunction and an elevated risk of atherosclerosis. Such vascular changes can directly damage brain tissue (i.e., white matter), leading to cognitive impairment. They may also lead to ischemic stroke, subsequently causing post-stroke dementia [48]. Additionally, both hyperglycemia and obesity are associated with insulin resistance and inflammation, which can cause overexpression of pro-inflammatory cytokines, and lead to neurodegeneration and neurotoxicity in brain tissue [49].

Strengths and limitations

The strengths of the present study include a population-based longitudinal study design with an adequate follow-up period and sample size, repeated measurement of MetS and its components, memory function and cognitive function, and con-

ducting a GWAS of MetS in a homogenous Chinese population. Additionally, different methodologies were used to verify the association of MetS with memory and cognitive decline (prospective cohort and MR studies), complemented by comprehensive adjustment for multiple potential confounders. However, several limitations should be acknowledged. Firstly, the sample sizes for the GWAS and MR analyses were relatively small compared to the overall cohort, which might have led to insufficient statistical power in detecting significant causal links between MetS and cognitive decline. Future studies with larger sample sizes are needed to validate our findings and potentially reveal stronger genetic associations. Meanwhile, our MR analysis might be constrained by the use of a limited number of SNPs to construct the weighted genetic score, potentially limiting the comprehensiveness of the genetic profile for MetS. Further studies could explore the use of polygenic risk scores that incorporate a larger number of SNPs to provide a more holistic genetic assessment. Secondly, the direction of the association of MetS with memory recall and registration appeared to be opposite, which could be due to the different assessment methods. Note that memory recall relies heavily on the ability to consolidate information, while registration involves simply repeating words. Additionally, a recent cohort study on 1,037 Australian adults examining the validity of the MMSE dimensions showed that orientation, attention and recall scores in the dementia group were significantly lower than those in the healthy group. In contrast, scores for registration and language did not differ significantly between the two groups [50]. This result suggests that MMSE dimensions may not be robust indicators of specific cognitive domains, such as language and registration, indicating the need for more specific neuropsychological tests to assess these aspects [50]. Therefore, memory recall is considered a more reliable indicator of memory function than registration. Regarding the language dimension, our unexpected results of a negative association between HDL-C and language underscores the necessity for future studies to use more specific tests for language and examine the association between MetS and language function. Thirdly, the history of diabetes was self-reported, and the lack of HbA1c measurement could lead to an underdiagnosis of preexisting diabetes, potentially confounding the observed associations between MetS components and cognitive decline. Finally, all GBCS participants were recruited in Guangzhou, which may not be representative of the general Chinese population. However, given that the prevalence of chronic diseases such as diabetes in our cohort was quite similar to the nationally representative samples of urban Chinese [17], the generalizability of our findings to a broader population might not be a concern.

In conclusion, our study showed a significant association of MetS and its components with declines in memory and cognitive function, especially in delayed memory recall. Given that Asia has a high prevalence of metabolic disease, our findings underscore the importance of effectively managing MetS and its components in older adults to delay or prevent cognitive impairment, with a specific emphasis on mitigating the impact on delayed memory recall.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0117.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: all authors.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: all authors.
Final approval of the manuscript: all authors.

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Ethical approval in place allows us to share data on requests. Please directly send such requests to the Guangzhou Biobank Cohort Study Data Access Committee (gbcsdata@hku.hk).

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SUPPLEMENTARY METHODS

DNA extraction and genotyping

The Guangzhou Biobank genetic data contains genotypes for 3,137 participants. DNA was extracted at the Guangzhou Twelfth People's Hospital from buffy coat stored at –80°C using a standard magnetic bead extraction procedure. Concentrations of DNA were examined by Nanodrop (Thermo Scientific, Waltham, MA, USA), and for those of <15 ng/μL, silica-based column method was used to re-extract DNA manually (Hipure Blood DNA Mini Kit, Magen Biotechnology, Guangzhou, China). We used the Illumina ASA (BeadChip Array Asian Screening Array-24+v1.0 HTS ASAMD-24v1-0, San Diego, CA, USA) genotyping platform (array). For ASA array (including 743,722 variants), 56.7% of the variants are common variants (with minor allele frequency [MAF] >0.05), 30.8% are low-frequency variant (with MAF between 0.01 and 0.05), and 12.5% are rare variants (MAF <0.01). ASA array includes a broad spectrum of pharmacogenomics markers (n=5,588) obtained from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (www.cpicpgx.org) and the Pharmacogenomics Knowledge Base (PharmGKB) database (www.pharmgkb.org). In addition, the ASA array contains about 50,000 single nucleotide polymorphisms (SNPs) selected from ClinVar database (www.ncbi.nlm.nih.gov/clinvar). More details about the ASA array can be found in the official Illumina website (https://www.illumina.com/products/by-type/microarray-kits). Genotyping assays were conducted at Guoke Biotechnology Co., LTD in Beijing, China (www.bioguoke.com).

Quality control

The quality control procedures of parameters for retaining SNPs and subjects were:

(1) SNPs with a call rate >97%;
(2) SNP missingness <0.02 (before sample removal);
(3) Samples with genotype missing rate <0.02;
(4) After checking the sex of sample, the F-value must <0.2 for women and >0.8 for men;
(5) SNPs with a MAF >0.01;
(6) SNP Hardy-Weinberg equilibrium (HWE) with $P>10^{-4}$ for samples;
(7) The participants of heterozygosity must remain ±3 standard deviation from the mean heterozygosity of all samples.

Genotype imputation

The imputation of the genotypes was performed by pre-phasing/imputation stepwise approach implemented in IMPUTE2/SHAPEIT (chunk size of 3 Mb and default parameters). The imputation reference set consisted of 2,504 samples with 5,008 phased haplotypes from the full 1000 Genomes Project dataset Phase 3 (update October 2014). Chromosome X (ChrX) imputation was conducted for subjects passing quality control for the autosomal analysis with the additional exclusions of chrX SNPs with missingness ≥0.05 or HWE $P<10^{-6}$ in females. ChrX imputation was performed separately for males and females.

Supplementary Table 1. Group-based trajectory model results of the fitting process

Variable	No. of groups	Log-Lik	BIC	Participants per group, %	Mean posterior probabilities
MetS index	1	−21,731.40	21,749.32	100	1.00
	2	−18,482.33	18,522.65	60.4/39.6	0.93/0.91
	3	−16,954.10	17,007.92	33.1/54.5/12.4	0.90/0.90/0.90
	4	−16,258.59	16,334.74	18.3/49.5/28.0/4.2	0.88/0.86/0.87/0.90
HDL-C	1	−16,802.35	16,820.27	100	1.00
	2	−13,139.25	13,184.04	86.4/13.6	0.97/0.90
	3	−11,483.95	11,546.66	71.8/23.8/4.4	0.94/0.88/0.96
	4	−10,871.50	10,956.61	54.3/34.2/7.7/3.8	0.89/0.81/0.86/0.95
SBP	1	−101,901.43	101,914.87	100	1.00
	2	−98,983.78	99,010.66	60.9/39.1	0.93/0.90
	3	−98,045.89	98,090.68	37.5/50.0/12.5	0.89/0.87/0.87
	4	−97,795.25	97,853.48	24.5/45.8/25.1/4.6	0.85/0.80/0.82/0.86
WC	1	−84,103.41	84,125.81	100	1.00
	2	−80,195.86	80,240.65	55.2/44.8	0.93/0.93
	3	−78,486.73	78,553.92	52.8/32.8/14.4	0.90/0.92/0.90
	4	−77,673.27	77,758.38	41.9/36.3/13.4/8.4	0.87/0.89/0.88/0.91
FPG	1	−40,876.87	40,899.27	100	1.00
	2	−35,258.09	35,302.89	94.9/5.1	0.99/0.97
TG	1	−35,657.00	35,674.92	100	1.00
	2	−31,685.77	31,726.08	95.2/4.8	0.99/0.94

Log-Lik, the maximum log-likelihood; BIC, Bayesian information criterion; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference; FPG, fasting plasma glucose; TG, triglyceride.

Supplementary Table 2. The 46 related SNPs from the GWAS of MetS involving 2,705 participants of the Guangzhou Biobank Cohort Study, 2003 to 2008

SNP	Nearest gene	Chr	Position	Risk/other allele	MAF, %	β	R^2	*P* value
rs662799	APOA5	11	116663707	G/A	28	0.4025	0.0467	1.67E-09
rs651821	APOA5	11	116662579	C/T	28	0.4011	0.0467	1.73E-09
rs7350481		11	116586283	T/C	28	0.3405	0.0385	6.82E-07
rs369326524		11	448280	C/A	1	1.3730	0.0019	7.44E-07
rs139017121	PTDSS2	11	468134	A/G	1	1.3730	0.0019	7.44E-07
rs6589566	ZNF259	11	116652423	G/A	23	0.3542	0.0334	9.17E-07
rs7483863	ZNF259	11	116652491	A/G	23	0.3542	0.0334	9.17E-07
rs2160669	ZNF259	11	116647607	C/T	22	0.3554	0.0324	9.17E-07
rs964184	ZNF259	11	116648917	G/C	23	0.3527	0.0333	1.02E-06
rs10750096	ZNF259	11	116656788	C/A	22	0.3530	0.0321	1.13E-06
rs10790162	BUD13	11	116639104	A/G	22	0.3494	0.0319	1.32E-06
rs6589565	BUD13	11	116640237	A/G	22	0.3494	0.0319	1.32E-06
rs9326246		11	116611733	C/G	23	0.3429	0.0328	1.44E-06
rs79605153		11	42820910	G/A	8	0.5446	0.0136	1.47E-06
rs138672212		11	42821674	T/G	8	0.5446	0.0136	1.47E-06
rs78160871		11	42824199	C/T	8	0.5446	0.0136	1.47E-06
rs2072560	APOA5	11	116661826	T/C	22	0.3484	0.0317	1.56E-06
rs146833250		11	42809333	G/A	8	0.5428	0.0136	1.59E-06
rs188079837		11	42812197	G/A	8	0.5428	0.0136	1.59E-06
rs187632323		11	42812408	G/A	8	0.5428	0.0136	1.59E-06
rs80036736		11	42799185	T/C	8	0.5420	0.0135	1.72E-06
rs140271395		11	42809205	C/T	8	0.5383	0.0135	1.91E-06
rs149979331		11	42790271	T/A	8	0.5375	0.0134	2.05E-06
rs76425601		11	42791477	C/T	8	0.5375	0.0134	2.05E-06
rs77699624		11	42798319	A/G	8	0.5375	0.0134	2.05E-06
rs74643618		11	42798127	T/G	8	0.5369	0.0134	2.10E-06
rs2266788	APOA5	11	116660686	G/A	23	0.3442	0.0323	2.12E-06
rs117738138		11	42802816	C/A	8	0.5363	0.0134	2.16E-06
rs1989154	HTR4	5	147848890	C/T	20	0.3837	0.0291	2.28E-06
rs74374343		11	42786965	G/A	8	0.5345	0.0134	2.32E-06
rs192379463		11	42804663	T/C	8	0.5337	0.0133	2.42E-06
rs3825041	BUD13	11	116631707	T/C	22	0.3422	0.0311	2.46E-06
rs1988819	HTR4	5	147849531	C/T	20	0.3814	0.0289	2.64E-06
rs10075211	HTR4	5	147839537	T/C	19	0.3863	0.0276	3.02E-06
rs12374521	HTR4	5	147836880	T/C	19	0.3883	0.0276	3.17E-06
rs80352262		7	47000652	A/G	0.6	1.6160	0.0011	3.26E-06
rs1558860		11	116607368	A/C	23	0.3296	0.0316	3.47E-06
rs4643960		5	84061741	T/C	24	–0.3576	–0.0324	3.73E-06

(*Continued to the next page*)

Supplementary Table 2. Continued

SNP	Nearest gene	Chr	Position	Risk/other allele	MAF, %	β	R^2	*P* value
rs76187712		11	42799721	T/C	8	0.5209	0.0131	3.81E-06
rs1974718		11	116606766	G/A	23	0.3282	0.0315	3.82E-06
rs1558861		11	116607437	A/C	24	0.3266	0.0324	3.89E-06
rs4133436		5	84062058	C/T	24	–0.3548	–0.0324	3.91E-06
rs6887366	HTR4	5	147851270	A/T	20	0.3729	0.0284	4.03E-06
rs2075290	ZNF259	11	116653296	C/T	25	0.3168	0.0330	4.64E-06
rs149595528		11	42814083	G/A	9	0.5128	0.0144	4.99E-06
rs77173973		11	42816900	A/G	9	0.5128	0.0144	4.99E-06

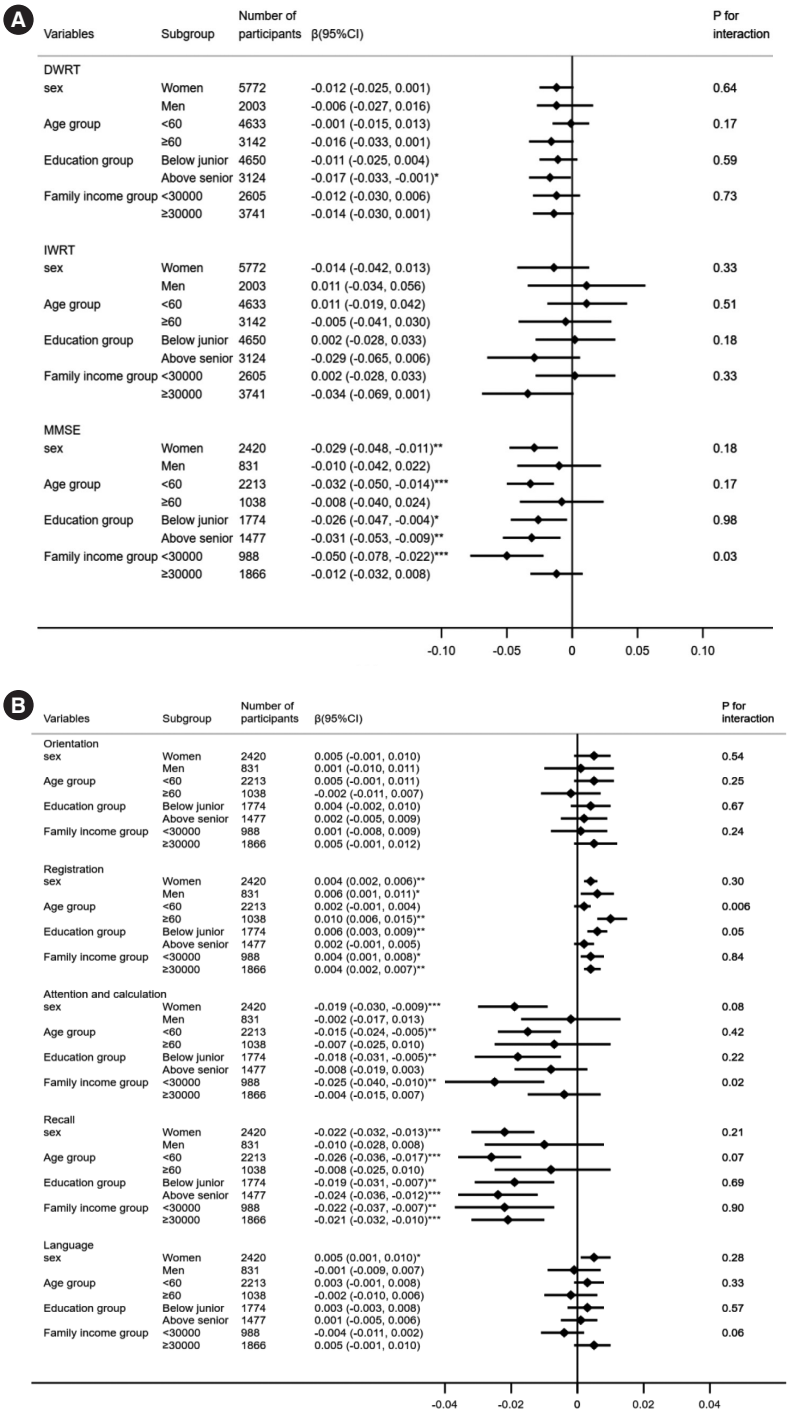
$R^2=2\times(1-\mathrm{MAF})\times\mathrm{MAF}\times\frac{\beta}{\mathrm{SD}}$; $\mathrm{SD}=\mathrm{SE}\times\sqrt{\mathrm{n}}$.

SNP, single nucleotide polymorphism; GWAS, genome-wide association study; MetS, metabolic syndrome; Chr, chromosome; MAF, minor allele frequency; APOA5, apolipoprotein A5; PTDSS2, phosphatidylserine synthase 2; ZNF259, zinc finger protein 259; BUD13, BUD13 homolog; HTR4, 5-hydroxytryptamine receptor 4.

Supplementary Table 3. Mendelian randomization instrumental variable analysis of the association of MetS with DWRT, IWRT, and MMSE scores in the Guangzhou Biobank Cohort Study, 2003 to 2008

Variable	No. of participants	β (95% CI)	*P* value
DWRT[a] MR (two-stage estimation, F-statistic=53)			
MetS[b]	2,613	–0.18 (–1.27 to 0.91)	0.74
IWRT[a] MR (two-stage estimation, F-statistic=53)			
MetS[b]	2,613	–1.28 (–3.68 to 1.13)	0.29
MMSE[a] MR (two-stage estimation, F-statistic=8)			
MetS[b]	677	–0.01 (–0.02 to 0.01)	0.98

MetS, metabolic syndrome; DWRT, delayed 10-word recall test; IWRT, immediate 10-word recall test; MMSE, mini-mental state examination; CI, confidence interval; MR, Mendelian randomization.
[a]β and 95% CI were adjusted for sex and age, [b]R^2 of the regression of MetS on instrumental variable was 0.0268.



Supplementary Fig. 1. Forest plots for the association between metabolic syndrome index and (A) the annual change rates in delayed 10-word recall test (DWRT), immediate 10-word recall test (IWRT), and mini-mental state examination (MMSE) scores and (B) five dimensions of MMSE stratified by sex, age group, education group, and family income group-based on linear mixed-effect model during 12-year follow-up. β and 95% confidence interval (CI) were adjusted for sex, age, baseline memory or cognitive function scores, body mass index, education, occupation, marital status, smoking status, drinking status, family income, physical activity, self-rated health, self-reported cardiovascular disease, hypertension, diabetes, hyperlipidemia, and drug history. MMSE consists of five dimensions: orientation, registration, attention and calculation, recall, and language.