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Metabolic syndrome increases the risk of suicide attempt: evidence from a population-based cohort and genomic analysis

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Suicide is a critical global public health issue, where traditional risk assessment tools have limited predictive value, warranting the identification of novel risk assessment factors. Metabolic syndrome (MetS) has been linked to poor cognition and brain volumes, which may lead to abnormal behaviors. The relationship between MetS and suicide risk has been less studied. This study aims to explore the association of MetS on suicide attempt leveraging data from the UK Biobank and genomic analyses. We first explored the cross-sectional and longitudinal relationships between MetS and suicide attempt, while also exploring the mediating role of cognitive performance. Second, using summary data from the largest genome-wide association studies, the genetic associations between MetS, suicide attempt, and cognitive performance were examined. Of 380,557 participants tracked over 13 years, we identified 1847 new cases of suicide attempt. The presence of MetS was found to significantly increase the risk of suicide attempt ($HR = 1.250$, 95% $CI = 1.134-1.379$). In participants lacking traditional suicide risk factors, such as being female, younger, and having higher educational attainment, MetS still presented a greater risk in predicting future suicide attempts. Additionally, MetS and suicide attempt exhibited significant genetic correlation ($rg = 0.080 \pm 0.026$), and Mendelian randomization analysis suggested MetS had a significant negative effect on suicide attempt ($\beta = 0.156$, 95% $CI = 0.077-0.235$). These findings highlight a significant association between MetS and increased suicide risk. Addressing MetS may offer an avenue for improved suicide management.

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INTRODUCTION

Suicide poses a significant public health challenge worldwide [1], culminating in more than 700,000 deaths annually [1, 2]. The cause of suicide is linked to complex factors, including genetic, socio-environmental, and psychopathological factors, rendering existing suicide risk assessment tools inadequate [1], with positive predictive values below 20% [3, 4]. Recent data indicate that in the UK, up to 90% of patients with mental disorders who died by suicide were assessed as having no risk or low risk of suicide by their clinical teams [5]. These facts underscore the urgent need for objective indicators to predict suicide risk at an early stage, especially in patients who lack traditional suicide risk factors. In response, the World Health Organization has initiated the Mental Health Action Plan, focusing on the development of prevention strategies that include identifying novel risk factors and early monitoring indicators [6].

Emerging evidence indicates a complex relationship between MetS and suicide risk. MetS and its components have been associated with structural and functional brain alterations, particularly in the reduction of volumes in regions crucial for emotion processing and cognitive function, such as the cingulate cortex and hippocampus [7, 8]. Notably, similar morphological changes have been observed in individuals with suicide behaviors [9]. In addition, MetS has been linked to systemic inflammation and oxidative stress [10, 11], which are increasingly recognized as important biological mechanisms in suicidal behaviors [12, 27].

Furthermore, MetS has been associated with cognitive impairment, particularly in the domains of executive function, processing speed, and memory [12–14]. These cognitive deficits correspond to those observed in individuals with suicidal behaviors, where impaired decision-making and cognitive flexibility have been identified as potential risk factors for suicide attempts [1, 12, 13, 15].

Recent studies examining the relationship between MetS and suicide risk have shown promising results, though findings vary across populations. A community-based study reported an up to an 88% higher risk of suicide attempts in individuals with MetS [16]. However, the relationship appears more complex when the presence of psychiatric disorders was considered [17, 18]. These mixed results may be partially explained by divergent methodological approaches and the potential mediating role of cognitive function, which has been independently associated with both MetS and suicide risk. Therefore, further exploration is needed to investigate the potential of MetS as an early indicator for monitoring suicide risk in the general population, with consideration of cognitive function as a mediating factor.

Based on these findings, this study aimed to investigate the relationship between MetS and suicide risk in the general population, specifically focusing on cognitive function as a mediator. We hypothesized that MetS would be associated with increased suicide risk and that cognitive function would mediate this relationship. To test these hypotheses, we utilized longitudinal

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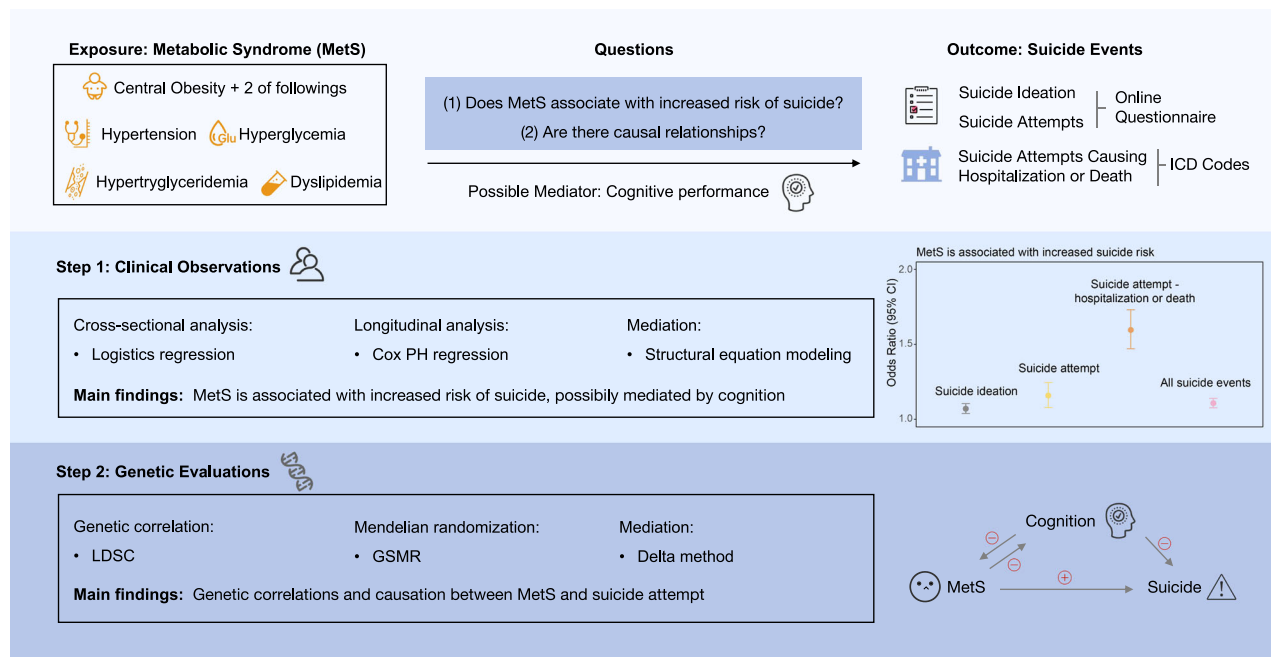


Fig. 1 The overall design of the study. This study aimed to identify the association between metabolic syndrome and suicide risk, as well as to investigate the mediating effect of cognitive function. The research consisted of two main parts. First, a population-based cohort study was conducted using UK Biobank data to examine the prospective association between metabolic syndrome and the risk of suicide attempt. Second, summary-level data from large-scale genome-wide association studies (GWAS) were used to explore the genetic correlation and potential causal relationship between metabolic syndrome and suicide risk.

data from the UK Biobank. Our objectives were to evaluate the potential of MetS as an objective indicator for monitoring suicide risk and to explore the underlying mechanisms linking metabolic health to suicidal behaviors.

METHODS

Ethics approval and study population

Ethical approval was obtained from the NHS National Research Ethics Service (11/NW/0382). Informed consent was obtained from each participant, before data collection. Our research utilized the prospective UK Biobank cohort initiated between 2006 and 2010. Initial evaluations collected individual-level information through self-administered questionnaires and a nurse-led verbal interview. Medical conditions were linked from the national death registration, hospital inpatient records, primary care data, and self-report health conditions during the assessment. Cognitive performance tests were assessed at the time of initial evaluation. All methods were performed in accordance with the relevant guidelines and regulations.

Figure 1 and Supplementary Fig. 1 present an overview of the study design. The initial cohort comprised 502,204 participants, all of whom underwent MetS screening during baseline evaluations. Participants were excluded if they lacked complete data for all five MetS diagnostic criteria ($n = 121,627$), resulting in 380,577 individuals eligible for suicide risk assessment. Online questionnaires identified 41,976 participants reporting suicide ideation or non-hospitalized suicide attempts. Through linkage with hospitalization records and mortality registries, 3493 participants were confirmed to have at least one suicide attempt resulting in hospitalization or death. We evaluated the MetS-suicide risk association using both cross-sectional and longitudinal analytic approaches, and assessed the mediating role of cognitive function. Data sources are detailed in Supplementary Table S1.

Definition of metabolic syndrome

MetS was defined in accordance with the criteria established by the International Diabetes Federation (IDF) [19]. Specifically, participants were diagnosed with MetS if they exhibited more than two of the following four components alongside evidence of central obesity: hypertension, hyperglycaemia, hypertriglyceridemia, and dyslipidemia for high-density lipoprotein (HDL) cholesterol.

Central obesity is defined as an unhealthy waist circumference or body mass index (BMI) $\geq 30 \text{ kg/m}^2$. The cut-off points for unhealthy waist circumference are $\geq 88 \text{ cm}$ for females, $\geq 94 \text{ cm}$ for males in Europeans, and $\geq 90 \text{ cm}$ for males of other ancestries. Hypertension was defined as a systolic blood pressure (SBP) $\geq 130 \text{ mmHg}$ or a diastolic blood pressure (DBP) $\geq 85 \text{ mmHg}$, or a history of treatment with antihypertensive drugs. Due to the limited number of participants with fasting glucose test results, hyperglycaemia was determined based on glycated haemoglobin (HbA1c) levels, with a cut-off point $>6\%$ (42 mmol/mol), aligning with the current study's strategy for evaluating MetS in the UK Biobank cohort [20]. Participants who received treatment with any antihyperglycemic drug were also classified as having hyperglycaemia. Hypertriglyceridemia was defined as $\geq 1.7 \text{ mmol/L}$ in triglyceride (TG) or a history of treatment with triglyceride-lowering drugs. Dyslipidemia was defined as HDL cholesterol levels $<1.03 \text{ mmol/L}$ in males and $<1.29 \text{ mmol/L}$ in females, or a history of treatment with cholesterol-lowering drugs. Codes for identifying the above drugs are listed in Supplementary Table S2.

When considering MetS as the exposure, it was treated as a binary variable (presence or absence of MetS). Additionally, we calculated the summed number for MetS traits and treated it either as an ordinal categorical variable (scores from 0 to 5, with 0 as the reference) to explore the risk of suicide attempt at each MetS score level, or as a linear variable to calculate the P value for trend.

Identification of suicide events

We used two source of data to identify suicide events: (1) Online mental-health questionnaires [21] and (2) Hospitalization and death registrations [22]. (1) The online questionnaires included "ever thought or contemplated suicide" (suicide ideation) and "ever attempted self-harm or suicide" (suicide attempt) without a specific time of events, therefore only allowing a cross-sectional analysis. The data fields for corresponding questionnaires are listed in Supplementary Table S1. (2) The hospitalization and death registrations recorded suicide attempts using the three-character International Classification of Disease (ICD) codes with corresponding times of event. Specifically, death by suicide was defined using the ICD-10 codes X60-84 and Y10-34 through the death registration. Suicide attempt causing hospitalization was defined using the ICD-10 codes X60-84 and ICD-9 codes E950-958 through hospital inpatient records. The time between the first suicide attempt either causing hospitalization or death and recruitment to the UK Biobank cohort was calculated in years. Suicide attempt before the

recruitment was considered as the suicide history. The primary outcome in this study was suicide attempt causing hospitalization or death.

Cognition data

To assess the mediating effect of cognitive performance on suicide attempt, we calculated a weighted cognitive z-score using the following five domains according to previous studies [23, 24]: fluid intelligence, numeric memory, reaction time, pairs matching, and prospective memory.

The fluid intelligence score was calculated as the unweighted sum of the number of correct responses to 13 fluid intelligence questions. Participants who failed to complete all items within the two-minute time limit received zero points for unanswered questions. Numeric memory tests involved sequential recall trials ranging from 2-digit to 12-digit sequences, with the longest correctly recalled sequence length recorded as the test outcome. In the reaction time assessment, paired cards were presented on the screen and the response latency of participant was measured when judging if the two cards were the same. Pairs matching test evaluated spatial working memory by requiring memorization of card positions, with performance quantified as the average number of correctly identified matching pairs. Prospective memory included an instructional phase where participants were directed: "At the end of the games we will show you four colored shapes and ask you to touch the Blue Square. However, to test your memory, we want you to touch the Orange Circle instead." The prospective memory result was coded as 0 for incorrect recall or skipped tests, 1 for correct recall on the second attempt, and 2 for correct recall on the first attempt.

Initially, we computed the z-score for each cognitive test. For reaction time, where higher values indicate worse cognitive performance, we inverted the values to align the directional interpretation with that of other cognitive tests. Subsequently, we applied a weighted averaging system for z-scores to ascertain the composite score of cognitive performance. The allocation of weights was determined by the number of tests each participant completed. Finally, we scaled the new scores to obtain the overall cognitive performance [23, 24].

Covariates

We incorporated four types of covariates when analyzing the impacts of MetS and the risk factors for suicide [14, 21]: (1) Basic demographic factors, including age at recruitment, sex, age², and educational level (categorized as high school equivalent or lower). (2) Household income as the socioeconomic factor. (3) Smoking status (categorized as never, former, or current smoker) as a lifestyle factor. (4) Significant suicide risk factors, including the number of previous suicide attempts and medical histories of schizophrenia, bipolar disorder, and major depressive disorder. When assessing the associations of cognition with MetS and its components, we adopted well-documented covariates including age, sex, age², and educational level. The correlations between these covariates and suicide attempt/MetS are shown in Supplementary Tables S3 and S4.

Among the 380,577 participants, 3963 lacked educational level, 1441 had missing smoking status records, and 54,739 were missing household income information. Missing covariates were imputed using the most frequent value (Supplementary Table S5). The coding strategies for the covariates are shown in Supplementary Table S6.

Sensitivity analysis

To investigate the predictive utility of MetS in individuals without traditional suicide risk factors, we conducted subgroup analyses stratified by suicide history (presence/absence), age groups (<55 years or ≥55 years), sex, educational attainment, smoking status, household income (median-dichotomized), and psychiatric histories (schizophrenia, bipolar disorder, or major depressive disorder).

Given documented elevated suicide attempt rates during the first two years post-recruitment in the UK Biobank and inherent data latency issues in registry linkages [22, 25], we excluded suicide cases recorded within two years after recruitment and re-performed the analyses. This sensitivity analysis aimed to disentangle potential measurement biases from the true biological associations.

Genetic correlation and Mendelian randomization

To assess the genetic associations between MetS, cognition, and suicide attempt, we obtained public summary data of Genome-wide association studies (GWAS) (Supplementary Table S7). The summary data of MetS was downloaded from the Complex Trait Genetics lab, with an estimated

sample size of 461,920 [26]. The summary data of cognitive performance was downloaded from the Social Science Genetic Association Consortium, with a total sample size of 257,818 [27]. The summary data of suicide attempt (including cases causing death) was obtained through the International Suicide Genetics Consortium, with a sample size of 815,178 [28]. All data were based on European ancestry with hg19 as the reference genome.

We used linkage disequilibrium score regression (LDSC) to access the genetic correlations between MetS, cognitive performance, and suicide attempt. Since all three summary data included participants from the UK Biobank, we used generalized summary-data based Mendelian randomization (GSMR) to interpret the potential genetic associations between these traits, which is unbiased by sample overlap between the exposure and the outcome [29]. GSMR was performed using GCTA software (Version 1.91.7), utilizing the Haplotype Reference Consortium (HRC) panel as the reference sample, and adopting a threshold P value of 5E-08 to select SNPs and an LD r^2 threshold of 0.01 for clumping analysis. The mediating effects of trait were estimated using the Delta method according to previous studies [30].

Statistical analysis

Statistical analyses were conducted using R software (Version 4.2.2). Continuous variables were summarized for description using mean values with standard deviations (SD) or median values with minimum to maximum values. Categorical variables were summarized using absolute counts and percentages. Comparisons between participants with or without suicide attempt were performed using Student's t-tests or chi-square tests.

Logistics regressions were performed to explore the cross-sectional relationships between MetS, suicide events, and cognitive performance. Cox proportional hazard models were performed to evaluate the impact of MetS on future suicide risk. Since participants may have multiple suicide attempts during the follow-up, we took the first suicide attempt as the endpoint. For those in the UK Biobank cohort without suicide attempt records, the study endpoint was defined by loss to follow-up or the data censoring date of November 2022. Linear regressions were used to assess the relationships between MetS and cognitive performance. To evaluate whether individual MetS components might be a better predictor for suicide risk than the integrated MetS diagnosis or a MetS composite score, we defined all 31 possible combinations of the five MetS components as exposure variables and accessed their strength of association with suicide risk and cognitive performance. The mediating effect of cognitive performance was explored using the *lavaan* package in R (Version 0.6-16). P values less than 0.05 were considered statistically significant.

RESULTS

Demographic characteristics

A total of 380,557 participants were included, the demographic characteristics are presented in Table 1. The mean age of the participants was 56.6 ± 8.09 years, and 53.8% (204,773) were female. The mean follow-up duration of this study was 13.3 ± 2.08 years. MetS was diagnosed in 32.7% (124,363) of the participants. 3493 (0.92%) participants had suicide attempts causing hospitalization, and 1847 (0.49%) occurred after recruitment. The presence of MetS was significantly higher in participants with subsequent suicide attempt (37.2%) than those without (32.7%, $P < 0.001$). In addition, participants with suicide attempt after recruitment were younger (53.6 ± 8.5 vs 56.6 ± 8.1 , $P < 0.001$) and had higher BMI (27.9 ± 5.4 vs 27.4 ± 4.8 , $P < 0.001$). The proportion of female was smaller (49.9 vs 53.8% , $P < 0.001$). For the social factors, participants with suicide attempt showed lower educational attainment (57.6 vs 66.2% , $P < 0.001$) and lower household income ($P < 0.001$). Suicide history was strongly associated with subsequent suicide attempt, with 12.6% of the participants with subsequent suicide attempt having a suicide history ($P < 0.001$).

Additionally, 32.5% (123,630 of the 380,577) of the participants completed the online mental-health questionnaires after recruitment, allowing us to identify life-time suicide ideation and attempt among this subgroup of participants. Among them, 33,649 (27.2%) participants reported a history of suicide ideation without actions, and 4834 (3.9%) participants reported suicide

Table 1. Comparison of baseline characteristics in participants with or without suicide attempt after recruitment.

	All participants (n = 380,557)	No suicide attempt after recruitment (n = 378,730)	Suicide attempt after recruitment (n = 1847)	P value
Sex (Female), n (%)	204,773 (53.8)	203,852 (53.8)	921 (49.9)	<0.001
Age in years, mean (SD)	56.6 (8.09)	56.6 (8.09)	53.6 (8.48)	<0.001
Body mass index in (kg/m ²), mean (SD)	27.4 (4.76)	27.4 (4.75)	27.9 (5.42)	<0.001
High school equivalent or more schooling, n (%)	251,596 (66.1)	250,532 (66.2)	1064 (57.6)	<0.001
Household income				<0.001
Less than 18,000, n (%)	73,755 (19.4)	73,138 (19.3)	617 (33.4)	
18,000 to 30,999, n (%)	82,687 (21.7)	82,305 (21.7)	382 (20.7)	
31,000 to 51,999, n (%)	139,829 (36.7)	139,201 (36.8)	628 (34.0)	
52,000 to 100,000, n (%)	66,517 (17.5)	66,330 (17.5)	187 (10.1)	
Greater than 100,000, n (%)	17,789 (4.67)	17,756 (4.68)	33 (1.79)	
Smoking status				<0.001
Never, n (%)	208,360 (54.7)	207,594 (54.8)	766 (41.5)	
Former, n (%)	132,304 (34.8)	131,742 (34.8)	562 (30.4)	
Current, n (%)	39,913 (10.5)	39,394 (10.4)	519 (28.1)	
Suicide history, n (n%)	1878 (0.5)	1646 (0.4)	232 (12.6)	<0.001
Metabolic syndrome, n (n%)	124,363 (32.7)	123,675 (32.7)	688 (37.2)	<0.001
Central obesity, n (n%)	233,461 (61.3)	232,267 (61.3)	1194 (64.6)	0.0038
Hypertension, n (n%)	271,632 (71.4)	270,351 (71.4)	1281 (69.4)	0.0578
Hyperglycemia, n (n%)	32,307 (8.5)	32,111 (8.5)	196 (10.6)	0.0012
Hypertriglyceridemia, n (n%)	153,496 (40.3)	152,649 (40.3)	847 (45.9)	<0.001
Dyslipidemia, n (n%)	64,078 (16.8)	63,729 (16.8)	349 (18.9)	0.0193

attempt that did not require hospitalization. Bold values indicate statistical significant.

MetS was associated with increased suicide risk

We first explored the cross-sectional associations between MetS and suicide risk (Fig. 2). The presence of MetS was associated with an increased trend in the risk of suicide ideation, suicide attempt without hospitalization, and suicide attempt causing hospitalization or death, with odds ratios (OR) and 95% confidence interval (CI) of 1.071 (1.040–1.105), 1.159 (1.079–1.246), and 1.596 (1.471–1.731), respectively (Fig. 2A, Supplementary Table S8). When considering all suicide events collectively, MetS remained significantly associated with an increased risk (OR = 1.108, 95% CI: 1.077–1.140).

A dose-response relationship was observed between the number of MetS traits and suicide events (Fig. 2B, Supplementary Table S9). Specifically, an increasing number of MetS traits was significantly associated with suicide attempt causing hospitalization or death (OR range: 1.227 to 3.577, P for trend $<2 \times 10^{-16}$). Participants fulfilled three or more traits of MetS showed a significantly increased risk of all suicide events (OR range: 1.088 to 1.352, P for trend = 2.37×10^{-12}).

We then assessed the longitudinal associations between MetS and subsequent suicide risk, by considering suicide attempt before recruitment as a covariate and taking the first suicide attempt causing hospitalization or death as the endpoint (Fig. 2C, Supplementary Table S10). The presence of MetS at baseline significantly increased subsequent suicide risk by 25.0% (Hazard ratio [HR]: 1.250, 95% CI: 1.134–1.379). There was also a dose-response relationship between the number of MetS traits and subsequent suicide risk (HR range: 1.160 to 1.501, P for trend = 3.84×10^{-6}).

To explore whether individual MetS components might be stronger predictors of suicide risk than the integrated MetS diagnosis or cumulative MetS traits, we evaluated all 31 potential

combinations of metabolic components (Supplementary Fig. 2). Elevated suicide attempt risk was observed for the combination of central obesity, hypertension, and dyslipidemia, which exceeded the hazard associated with MetS alone. However, these combinations did not significantly outperform other three-component configurations.

Cognitive performance serves as a mediator from MetS to suicide risk

We further questioned whether the relationships between MetS and suicide risk was mediated by cognitive performance. Among the five cognitive domains assessed at baseline, enhanced performance was associated with lower suicide risk (Supplementary Table S11). We identified bidirectional relationships between MetS and cognition: MetS predicted poorer cognitive performance across all domains (Supplementary Table S12), while higher baseline cognition correlated with reduced incident MetS risk (Supplementary Table S13).

In addition, cumulative MetS components demonstrated a graded inverse relationship with global cognition (Supplementary Table S14). The combination of hyperglycemia, dyslipidemia, and central obesity exhibited stronger cognitive detriment that exceeding the predictive power of simple MetS component counts for pairs matching results (Supplementary Fig. 3).

We then calculated the weighted average of the five cognitive domains to represent the overall cognitive function, and subsequently analyzed its associations with MetS and suicide attempt (Fig. 3A, Supplementary Table S15). We found the presence of MetS was associated with impaired overall cognitive performance ($\beta = -0.065$, 95% CI: -0.072 – -0.058). Conversely, enhanced overall cognitive performance demonstrated an inverse relationship with the likelihood of MetS (OR = 0.933, 95% CI: 0.927–0.940). In addition, both MetS (OR = 1.248, 95% CI: 1.160–1.342) and the overall cognitive performance (OR = 0.873, 95% CI: 0.851–0.895)

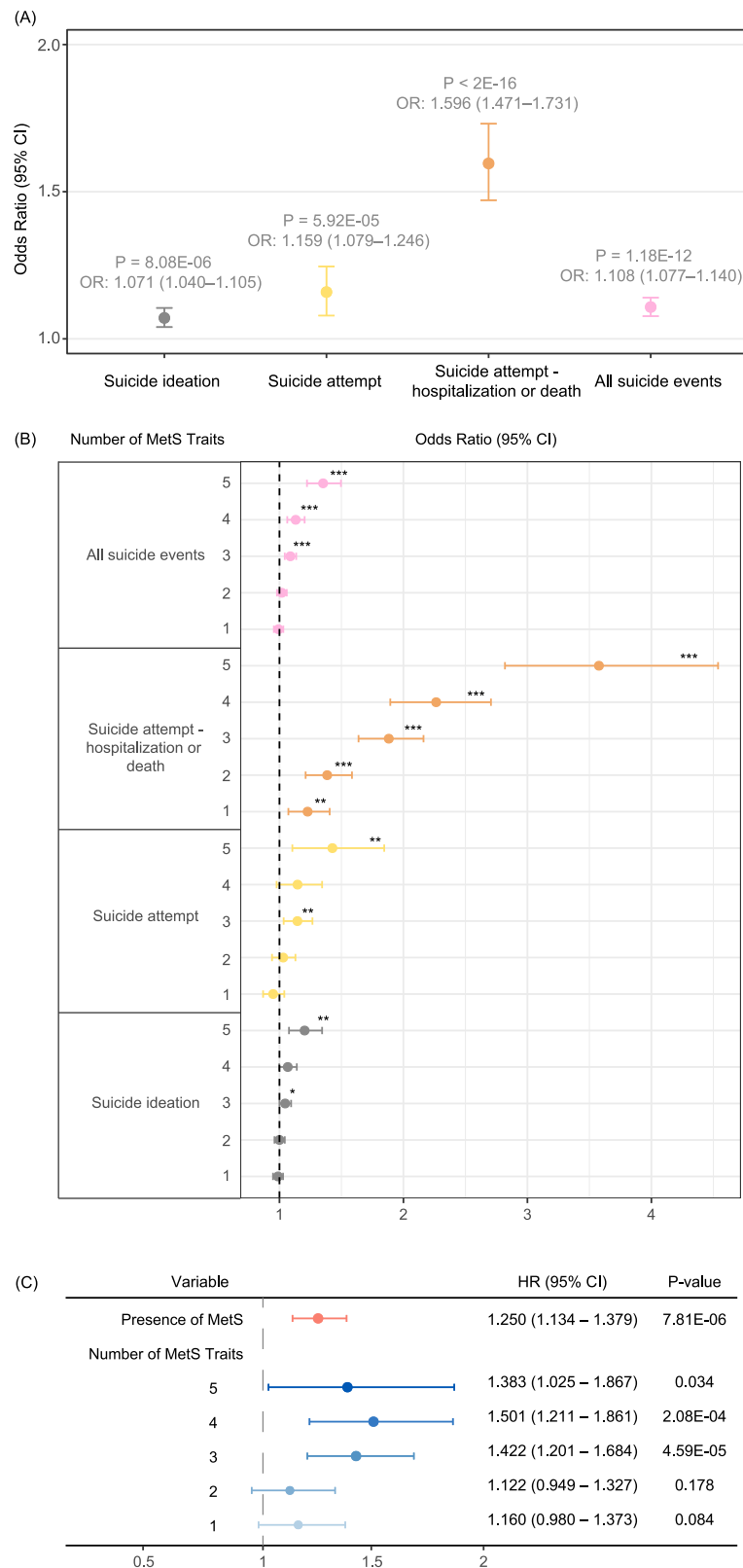


Fig. 2 Associations between metabolic syndrome and suicide events. A, B Define suicide events using online mental-health questionnaires, using logistics regressions; **A** Taking metabolic syndrome as a binary variable. **B** Using the number of components of metabolic syndrome as an independent variable. **C** Define suicide attempt using hospitalization records and death registration, using cox regressions. *P value < 0.05, **P value < 0.01, ***P value < 0.001.

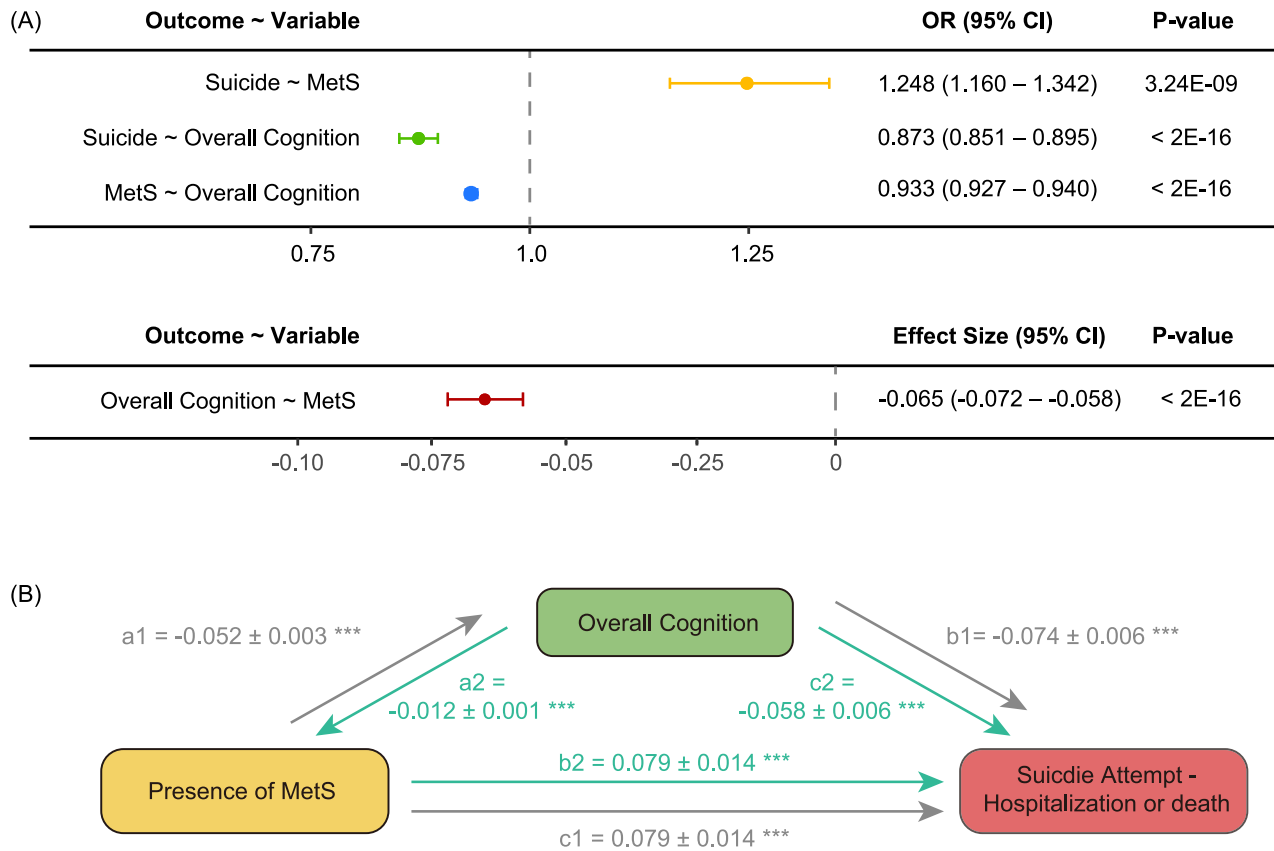


Fig. 3 Mediating effects of metabolic syndrome and cognitive performance. **A** Associations between the presence of metabolic syndrome, overall cognitive performance, and lifetime suicide attempt causing hospitalization or death. **B** Results of mediation analyses. Grey lines illustrate path 1 (metabolic syndrome to cognitive performance, then to suicide attempt). Green lines illustrate path 2 (cognitive performance to metabolic syndrome, then to suicide attempt). c_1 and c_2 are the direct effects.

exhibited significant associations with lifetime suicide attempt resulting in hospitalization or death.

We then performed mediation analysis to dissect the relationships between MetS, overall cognitive performance, and suicide attempt (Fig. 3B). Cognitive performance may mediate the association between MetS and suicide attempt, while it could also reduce suicide risk by affecting MetS.

Sensitivity analyses

We performed sensitivity analysis by stratifying participants based on their suicide histories (Supplementary Table S16) and found that the presence of MetS significantly increased the risk of subsequent suicide attempt in participants without suicide histories (HR = 1.247, 95% CI: 1.122 – 1.385).

When grouping by age, sex, educational level, smoking status, and household income, the presence of MetS was identified as a significant risk factor for subsequent suicide attempt, except for current smokers, in whom MetS only showed a trend towards increasing suicide risk ($P = 0.225$). In addition, we found the impact of MetS on suicide attempt was higher than the general level in participants who were younger (< 55 years, HR = 1.378, 95% CI: 1.201–1.581), female (HR = 1.378, 95% CI: 1.191–1.595), had higher educational attainment (HR = 1.289, 95% CI: 1.131–1.470), and did not present medical history of major psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder (HR = 1.427, 95% CI: 1.075–1.894). These results suggest that MetS could be used as a supplementary indicator for the monitoring of suicide risk in those without traditional suicide risk factors.

Lastly, we excluded participants with their suicide attempt recorded within two years after recruitment, and found that the

presence of MetS was still associated with an increase risk of suicide attempt (HR = 1.275, 95% CI: 1.143–1.423).

Genetic associations between MetS and suicide attempt

We utilized the largest GWAS summary data for MetS, cognitive performance, and suicide attempt (including cases causing death) to explore their genetic relationships (Fig. 4). We found suicide attempt was genetically correlated with both MetS ($rg = 0.080 \pm 0.026$, $P = 0.002$) and cognitive performance ($rg = -0.213 \pm 0.026$, $P = 3.86 \times 10^{-16}$). There was also a significant genetic correlation between MetS and cognitive performance ($rg = -0.133 \pm 0.019$, $P = 1.02 \times 10^{-12}$) (Fig. 4A, Supplementary Table S17).

Mendelian randomization using GSMR suggested significant effects of MetS ($\beta = 0.156$, 95% CI: 0.077 – 0.235) and cognitive performance ($\beta = -0.109$, 95% CI: -0.183–0.036) on suicide attempt. In addition, MetS and cognitive performance suggested bidirectional effects on each other (Fig. 4B, Supplementary Table S18, Supplementary Fig. 4). The mediation analysis indicated that cognitive performance was a mediator linking MetS and suicide attempt, with a mediated proportion of 8.96%. On the other hand, better cognitive performance decreased the risk of suicide attempt, which was mediated by MetS with a mediated proportion of 21.94% (Fig. 4C, D, Supplementary Table S18).

DISCUSSION

This study represents a pioneering analysis of the correlation between MetS and suicide attempt by combining evidence from a population-based cohort and genetic data. We found that the presence of MetS at baseline is a significant risk factor for future suicide actions, and cognitive performance and MetS exhibit

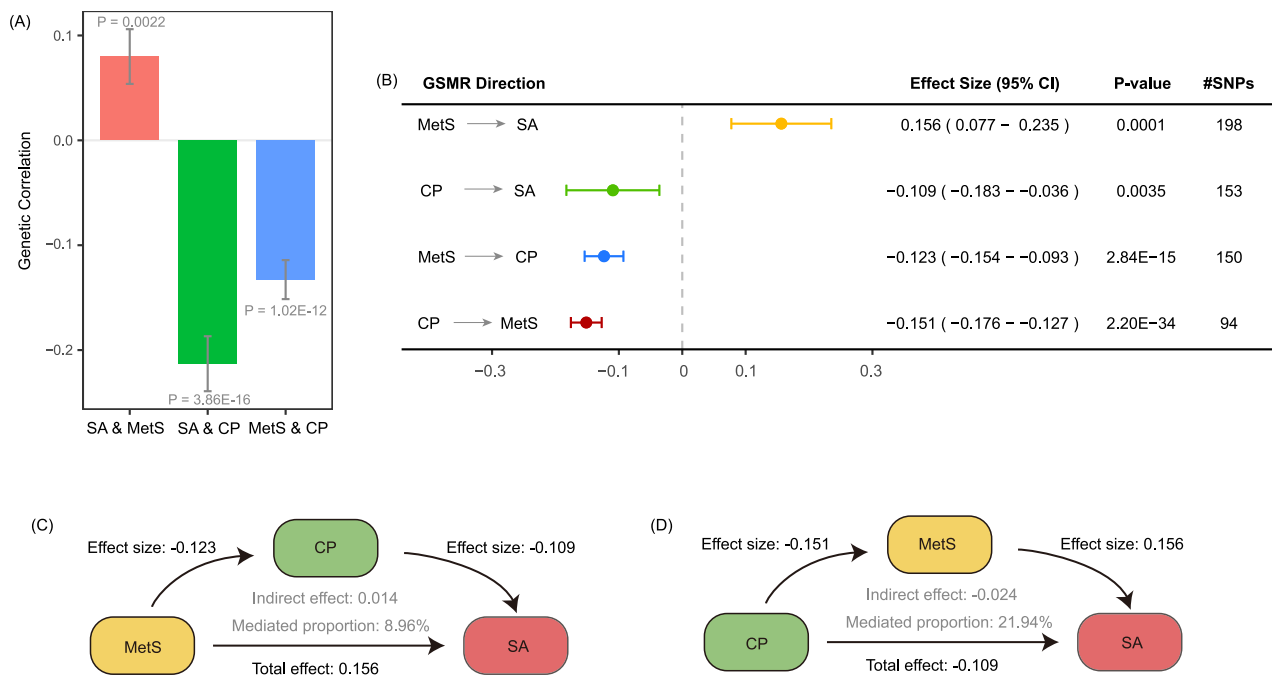


Fig. 4 Genetic analyses for the associations between metabolic syndrome, cognitive performance (CP), and suicide attempt (SA). **A** Genetic correlations. **B** Mendelian randomization analyses using GSMR. **C, D** Mediation analysis using Delta method.

bidirectional mediation in affecting future suicide risk. Our findings collectively suggest that MetS could be used as a modifiable factor in the monitoring and management of suicide risk.

The high prevalence of MetS brings major concerns to the public health. Besides affecting cardiovascular outcomes and all-cause mortality [31], recent evidence has linked MetS to worse brain health [14]. For instance, Qureshi et al. confirmed that MetS was associated with less brain volume and poor cognition in over 37,000 participants [14]. Since damage to brain health is one of the major causes of suicide, it is possible that MetS could be a novel risk factor for suicide.

Although several studies have reported the associations between MetS and suicide, most of them were conducted in specific populations (such as patients with psychiatric disorders) and yield inconsistent results [32]. Chang et al. reported that MetS was associated with a 88% increase in the risk of suicide death through a community-based cohort [16]. Mellor et al. reported that young individuals who attempted suicide were twice as likely to have comorbid MetS [18]. However, Stenzel et al. discovered that in patients with bipolar disorders, MetS was not linked to suicide [17]. It is possible that the limited sample size, heterogeneity of study population, and presence of confounding factors (such as socio-environmental factors and suicide history) lead to the controversial findings. Our study, leveraging the longitudinal cohort of the UK Biobank and focusing on over 380,000 participants, provides more robust results. Furthermore, our subgroup analyses revealed that MetS was associated with a higher suicide risk among females, those of younger age, had higher educational attainments, and without histories of suicide or psychiatric disorders, which have previously been considered protective factors against suicide [1]. While individuals lacking these traditional risk factors might typically be assessed as having low suicide risk, the presence of MetS could serve as a valuable supplementary indicator in suicide risk evaluation.

Our study found that MetS was associated with poor cognitive performance and that it exhibits bidirectional mediation in promoting suicide attempts. This phenomenon can be explained through several biological mechanisms. First, studies demonstrate

that MetS may induce endothelial dysfunction, resulting in compromised cerebral blood flow regulation [33]. This vascular dysfunction is often accompanied by the disruption of the blood-brain barrier, allowing neurotoxic substances to enter the central nervous system, directly causing white matter damage that is strongly associated with cognitive decline [33, 34]. Second, MetS typically involves chronic systemic inflammation with elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) [35, 36]. Our previous study has shown that elevated plasma IL-6 levels correlated with both brain volume loss and cognitive decline, as well as an increased risk of dementia [37]. Third, the five components of MetS appear to independently influence cognitive performance through distinct pathways; for instance, hyperglycemia has been shown to impair the cerebral energy metabolism and promote neuronal dysfunction [38].

Conversely, impaired cognitive function may also promote the development of MetS. First, impaired cognition may trigger reward-seeking behaviors, including unhealthy dietary choices and sedentary behaviors, directly exacerbating MetS [39]. Second, cognitive decline leads to chronic hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, including abnormally elevated cortisol levels [40]. This endocrine imbalance promotes central adiposity, insulin resistance, and dyslipidemia through overactivation of glucocorticoid receptor, all of which are key components of MetS [41]. Notably, chronic stress activation leads to an increase in inflammatory cytokines, which contribute to the development of both MetS and cognitive decline [41]. Collectively, these interconnected mechanisms create a deleterious feedback loop between cognitive decline and the progression of MetS.

Our subgroup analyses demonstrate that MetS elevates suicide risk across all demographic strata, including traditionally protected populations, mediated by distinct mechanisms operating across sex, age, and education. We propose several potential explanations for these findings. First, women with MetS experience greater societal pressure, such as social stigma [42], which may contribute to increased psychological distress and suicide risk [43]. Second, younger adults with MetS exhibit accelerated white matter hyperintensity progression and early-onset prefrontal metabolic dysregulation [44, 45], and disproportionately executive

functions [46]. Regarding individuals with higher educational attainment, they may have stronger identity ties to their intellectual capabilities, making cognitive decline more perceptible and threatening to their self-concept and social-status maintenance, thereby intensifying their psychological burden [47–49].

Our genetic analyses revealed a significant genetic correlation between MetS and suicide attempt, and Mendelian randomization analysis indicated that MetS plays a negative effect on suicide attempt. These findings should be interpreted within the broader context of familial influences on suicide risk. Research has shown that suicide attempts have a substantial heritability, ranging from 41 to 55% [50], with individuals having a family history of suicide showing up to three times higher risk of suicide attempt [51]. However, genetic predisposition to suicide does not operate alone but rather interacts substantially with environmental factors [15].

The influence of MetS on suicide risk may function via two mechanisms: gene-environment interaction (GxE) and gene-environment correlation. Regarding GxE, individuals with increased genetic susceptibility to suicide may experience an elevated risk when they develop MetS [52, 53]. Additionally, environmental factors commonly shared among family members—such as dietary habits, lifestyle patterns, and socioeconomic status—contribute to both MetS and suicide risk. Thus, the observed association between MetS and elevated suicide risk might be attributable to socioeconomic factors that directly influence suicide risk. Furthermore, recent genome-wide association studies have identified substantial genetic overlap between suicide attempts and various psychiatric disorders, suggesting shared biological pathways [54]. The significantly higher prevalence of MetS in patients with psychiatric disorders may partially explain these findings. Moreover, individuals with a family history of suicide often face social stigma and bullying [55], which may not only lead to depression or suicidal ideation but also trigger emotional eating, potentially contributing to MetS [56]. Conversely, social stigma associated with individuals who have obesity or are overweight conditions may increase vulnerability to mental disorders and suicide [43]. However, due to the unavailability of family suicide history data in the UK Biobank, we could not definitively establish a relationship between family history of suicide and MetS. This aspect warrants investigation in future studies.

As a modifiable factor, interventions on MetS and its components have shown protecting effects on brain health [14]. Unfortunately, there is lack of evidence regarding the effects of managing MetS on suicide risk. A recent meta-analysis of randomized controlled trials indicated that exercise decreased the risk of suicide attempt by 77% [57], which is a promising result that supports the potential benefits of targeting MetS for managing suicide risk. Further intervention studies are needed to understand whether the reversal of MetS can reduce suicide risk.

There are several limitations of this study. First, the high educational level among UK Biobank participants, compared to the general population, may limit the generalizability of our findings, as education is a protective factor against suicide. Second, we did not perform a comprehensive mediator analysis between MetS and suicide attempt. Third, the lack of longitudinal MetS data restricts our ability to determine whether improvements in MetS correlate with decreased suicide risk. Furthermore, since the brain imaging data of the UK Biobank was acquired six years after participant recruitment, and most of the suicide occurred within the six years post-recruitment [22], we were unable to access the mediating role of brain structures in the pathway from MetS to suicide. In our mediation analysis examining cognition as a mediator, we calculated weighted averages for cognitive domains, applying equal weights to construct the overall cognitive score. However, given that certain

domains demonstrated stronger associations with suicide than others, an alternative approach could have been to weight the cognitive results based on their respective associations with suicide risk. Most importantly, although family history of suicide is one of the strongest predictors of suicide attempt, we were unable to obtain this information in the UK Biobank dataset. Future studies should aim to address these gaps.

CONCLUSION

In conclusion, this study contributes to the understanding of MetS in increasing suicide risk. MetS could be a complementary indicator in the prediction and early intervention of suicide risk.

DATA AVAILABILITY

Raw data can be accessed following approval from the UK Biobank team. Statistical data are available in the Supplementary Tables. Q.W. and Z.Z. are the guarantor of this work, and such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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AUTHOR CONTRIBUTIONS

QW contributed to the conception and design of the study. QW, and ZZ contributed to the data analysis and interpretation, and drafted the manuscript. MX, JC, ST, QL, and JZ critically reviewed and edited the manuscript. YL, YH, SL, and YW contributed to the interpretation of the data. QW, MX, JC, ST, and ZZ obtained the funding. All authors approved the final version of the manuscript. QW and ZZ are the guarantor of this work, and such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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COMPETING INTERESTS

The authors declare no competing of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The UK Biobank study received approval from the National Health Service North West Multicenter Research Ethics Committee. All participants were informed of consent via electronic signature prior to participation in the study.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41398-025-03575-1>.

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