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FULL RESEARCH PAPER
Social-psychological factors

Increased cardiovascular events in young patients with mental disorders: a nationwide cohort study

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Aims It remains unclear whether young patients with mental disorders have a higher risk of cardiovascular diseases than does the general population. Using a nationwide database, we investigated the prognostic association between the risks of myocardial infarction (MI), ischaemic stroke (IS), and mental disorders in young patients.

Methods and results Young patients aged between 20 and 39 years old who underwent nationwide health examinations between 2009 and 2012 were screened. A total of 6 557 727 individuals were identified and subsequently classified according to mental disorders including depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. Patients were then followed up for MI and IS until December 2018. Patients with mental disorders did not show unfavourable lifestyle behaviours or worse metabolic profiles than their counterparts. During the follow-up period (median, 7.6 years; interquartile range, 6.5–8.3), 16 133 cases of MI and 10 509 cases of IS occurred. Patients with mental disorders had higher risks of MI (log-rank $P = 0.033$ in eating disorder and log-rank $P < 0.001$ in all other mental disorders). Patients with mental disorders had higher risks of IS except post-traumatic stress disorder (log-rank $P = 0.119$) and eating disorder (log-rank $P = 0.828$). After adjusting for covariates, the overall diagnosis and each mental disorder were independently associated with increased cardiovascular endpoints.

Conclusion Mental disorders in young patients may have deleterious effects which increase the incidence of MI and IS. Prevention efforts are needed to prevent MI and IS in young patients with mental disorders.

Lay summary Although young patients with mental disorders did not show worse baseline characteristics in this nationwide study, mental disorders in young patients have deleterious effects on the incidence of both myocardial infarction (MI) and ischaemic stroke (IS) events, across depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorders, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder.

- Patients with mental disorders are known to have a shorter life expectancy across schizophrenia, affective disorders, and other mental disorders than the general population; previous study verified that around 70% of deaths in those with mental disorders were due to physical diseases. If patients with mental disorders have higher risks of cardiovascular diseases, especially in young patients, prevention and surveillance of cardiovascular diseases among these young patients during their lifetime should be considered.
- A substantial number of young patients aged 20–39 years (13.1%) were diagnosed with mental disorders, and excessive risks of incident MI and IS were observed in patients with mental disorders including depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. In contrast to previous suggestion that unfavourable lifestyle behaviours

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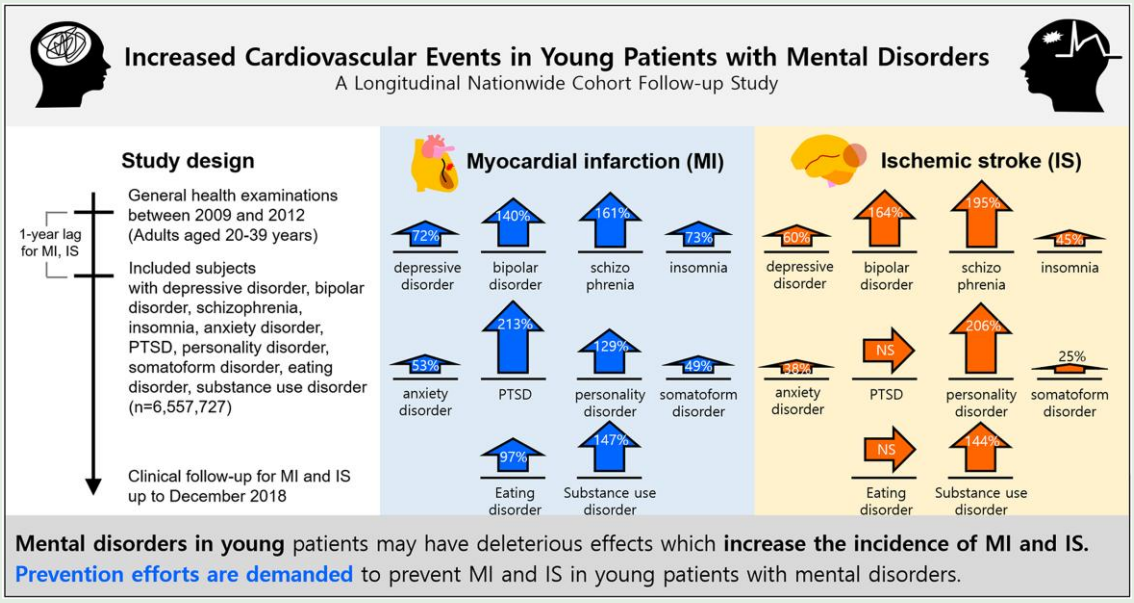
and poor cardiometabolic profiles could lead to increased cardiovascular risks, patients with mental disorders did not show unfavourable lifestyle behaviours or worse metabolic profiles than their counterparts.

Graphical Abstract



Keywords Mental disorders • Prognosis • Myocardial infarction • Ischaemic stroke

Introduction

Patients with mental disorders are known to have a shorter life expectancy across schizophrenia, affective disorders, and other mental disorders than the general population.[1–4] The majority of the excess mortality of mental disorders cannot be fully explained by factors such as drug abuse or suicide.[4,5] Notably, the mortality gap has risen over the decades.[6,7] Considering the widespread prevalence of mental disorders across countries and ethnicities,[8,9] there is a substantial demand to improve the clinical prognosis of patients with mental disorders. A previous study showed that lengthening life expectancy in the general population mainly drives the increasing mortality gap[10]; it could be speculated that patients with mental disorders receive fewer benefits from advanced medical treatment of other physical diseases.[11]

Cardiovascular diseases, including myocardial infarction (MI) and ischaemic stroke (IS), are among the leading causes of death worldwide.[12,13] Several studies have reported that physical diseases, including cardiovascular diseases, were more frequently observed in patients with mental disorders than in their counterparts.[5,7,14] Based on this, there have been concerns whether mental disorders in young people could lead to increased risks of cardiovascular events and poor prognosis in their lifetime.[15] Although some studies have investigated the impact of mental disorders on cardiovascular risks in young people, these studies often included a small number of persons and dealt with surrogate markers (i.e. metabolic profiles) rather than clinical outcomes.[16–19] Hence, there is still an unmet clinical need to unveil the associations between mental disorders and cardiovascular events in young persons.

We aimed to investigate the association between mental disorders and cardiovascular events, specifically MI and IS in young persons. To address this, we used a nationwide cohort to investigate the association between the risks of MI, IS, and various mental disorders including depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder in young patients.

Methods

Ethical statement and data availability

The study was conducted in accordance with the Declaration of Helsinki and approved by our institutional review board (IRB No. E-2110–109-1264). The need for informed consent was waived as anonymized data were used. All raw data were accessible from designated terminals approved by the National Health Insurance Service (NHIS). For a reasonable request, data are available through approval and oversight by the Korean NHIS.

Data source and study population

This nationwide population-based cohort study used data from the Korean NHIS database. Reports regarding the NHIS database have been published elsewhere.[20] In brief, the NHIS is a single public insurer that covers the entire Korean population and encourages eligible Korean adults to receive general health checkups provided by the NHIS. Therefore, the NHIS database includes individual demographic information, history of diagnoses, and the results of health checkups. Individuals' medical history was coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).

The flowchart of the study is shown in *Figure 1*. We identified 6 891 399 adults aged 20–39 years who underwent general health examinations between 1 January 2009 and 31 December 2012. We excluded patients with a history of MI and/or IS before the public health examination.

Individuals with missing data during general health checkups were also excluded from the study. Among the 6 562 082 screened individuals, 6 557 727 were finally included after a 1-year lag for MI and IS. Subjects were followed up until December 2018, and data on baseline characteristics were collected from the date of the general health examination (index date).

Definitions of mental disorders

We investigated whether cardiovascular risks of MI and IS increased in patients with depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. Each mental disorder was defined when the subject had claims for mental disorders in the NHIS database; persons could be diagnosed with depressive disorder (ICD-10-CM codes F32 and F33), bipolar disorder (ICD-10-CM codes F30 and F31), schizophrenia (ICD-10-CM code F20), insomnia (ICD-10-CM codes F51 and G47), anxiety disorder (ICD-10-CM codes F40 and F41), post-traumatic stress disorder (ICD-10-CM code F43.1), personality disorder (ICD-10-CM code F60), somatoform disorder (ICD-10-CM code F45), eating disorder (ICD-10-CM code F50), and substance use disorder (ICD-10-CM codes F10–F19) according to their medical history.

Definitions of covariates and clinical endpoints

The date of the general health examination for each patient was designated as the index date. Demographic data, anthropometric data, and history of hypertension, diabetes mellitus, dyslipidaemia, metabolic syndrome, and chronic kidney disease were all obtained. In addition, a self-report questionnaire was used to collect patient alcohol consumption and physical activity data.[21,22] Specifically, the average alcohol intake per day (g/day) was analysed to evaluate alcohol consumption, and the subjects were subsequently categorized as non-, mild (<30 g/day), and heavy (≥30 g/day) drinkers. The duration and number of sessions of moderate- and vigorous-intensity physical activity per week (/week) were evaluated to categorize the degree of regular physical activity. Regular physical activity was defined as performing moderate-intensity exercise for more than 30 min ≥ 5 days/week or vigorous-intensity exercise for more than 20 min ≥ 3 days/week.

Newly diagnosed cardiovascular events of MI and IS after a 1-year lag period were defined as the study endpoints (*Figure 1*). Myocardial infarction was diagnosed using ICD-10-CM codes I21 and I22, with more than one diagnosis during admission. Ischaemic stroke was defined by the diagnosis of ICD-10-CM codes I63 and I64 with hospitalization and concomitant brain imaging studies, involving computed tomography or magnetic resonance image. Detailed definitions of comorbidities are provided in Supplementary material online, *Table S1*.[23,24] The follow-up duration was defined as the interval between the index date and the first occurrence of cardiovascular endpoints for participants who experienced incident MI and IS. For participants without incident MI and IS, the follow-up duration was defined as the interval between the index date and December 2018.

Statistical analysis

Data are presented as numbers and frequencies for categorical variables and as means ± standard deviations or medians with interquartile ranges for continuous variables. χ^2 or Fisher's exact test was used for categorical variables, where appropriate. The annual event incidence rate (IR) was calculated as the number of events per 100 000 person-years (PY). The chronological trends of MI and IS were presented with Kaplan–Meier survival curves and analysed using a log-rank test according to the presence of mental disorders. Multivariate Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for the associations between mental disorders and cardiovascular outcomes. Multivariable models were adjusted for covariates including age, sex, previous history of hypertension, diabetes mellitus, dyslipidaemia, metabolic syndrome, chronic kidney disease, current smoking, heavy alcohol consumption, regular physical activity, and low income. Subgroup analyses were conducted separately based on age and sex. A two-sided *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the study population

Of the 6 557 727 included subjects, 856 927 (13.1%) were diagnosed with a mental disorder. The mean age was 30.9 ± 5.0 years, and 3 790 630 (57.8%) subjects were aged 30 years or older. Hypertension

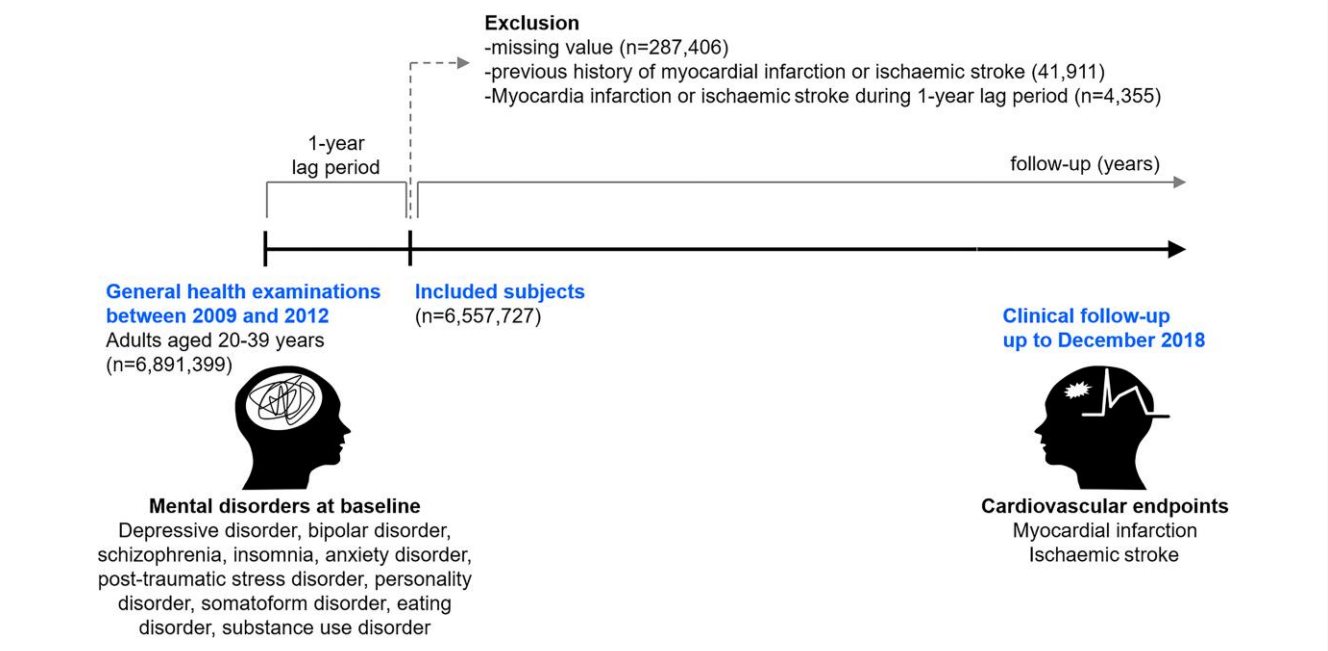


Figure 1 Study flowchart.

was present in 483 271 (7.4%) of subjects, diabetes mellitus in 128 842 (2.0%), dyslipidaemia in 454 807 (1.6%), metabolic syndrome in 708 944 (10.8%), and chronic kidney disease in 103 809 (1.6%).

The baseline characteristics of the subjects with and without mental disorders are shown in *Table 1*. Among the patients diagnosed with mental disorders, depressive disorder was diagnosed in 181 697 (21.2%), bipolar disorder in 10 800 (1.3%), schizophrenia in 7450 (0.9%), insomnia in 171 785 (20.0%), anxiety disorder in 410 250 (47.9%), post-traumatic stress disorder in 3038 (0.4%), personality disorder in 5572 (0.7%), somatoform disorder in 238 815 (27.9%), eating disorder in 7441 (0.9%), and substance use disorder in 23 062 (2.7%). The baseline characteristics for each mental disorder are presented in Supplementary material online, *Tables S2–S11*.

Persons with and without mental disorders were diagnosed with hypertension (7.1% vs. 7.4%), diabetes mellitus (2.0% vs. 2.0%), dyslipidaemia (7.1% vs. 6.9%), metabolic syndrome (10.1% vs. 10.9%), and chronic kidney disease (1.2% vs. 1.7%). Regarding lifestyle behaviours, current smoking (28.5% vs. 35.9%), heavy alcohol consumption (7.9% vs. 9.0%), and regular physical activity (13.1% vs. 12.9%) were observed in persons with and without mental disorders.

Table 1 Baseline characteristics according to mental disorders

	Without mental disorders ($n = 5\,700\,800$, 86.9%)	With mental disorders ($n = 856\,927$, 13.1%)	*P*-value
Demographic data			
Age, years	30.8 ± 5.0	31.4 ± 5.0	<0.0001
Male, %	3 505 863 (61.5)	398 858 (46.6)	<0.0001
BMI, kg/m^2	23.1 ± 3.6	22.7 ± 3.6	<0.0001
Comorbidities, %			
Hypertension	422 647 (7.4)	60 624 (7.1)	<0.0001
Diabetes mellitus	111 508 (2.0)	17 334 (2.0)	<0.0001
Dyslipidaemia	393 855 (6.9)	60 952 (7.1)	<0.0001
Metabolic syndrome	622 447 (10.9)	86 497 (10.1)	<0.0001
Chronic kidney disease	93 882 (1.7)	9927 (1.2)	<0.0001
Physical examination			
SBP, mmHg	118.0 ± 13.2	116.2 ± 13.1	<0.0001
DBP, mmHg	73.9 ± 9.5	72.9 ± 9.4	<0.0001
Social history, %			
Low income	880 179 (15.4)	153 797 (18.0)	<0.0001
Current smoking	2 045 336 (35.9)	244 115 (28.5)	<0.0001
Heavy alcohol consumption	510 389 (9.0)	67 632 (7.9)	<0.0001
Regular physical activity	732 899 (12.9)	112 061 (13.1)	<0.0001

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Excessive risks of myocardial infarction and ischaemic stroke in young patients with mental disorders

During a median follow-up of 7.6 years (interquartile range, 6.5–8.3), 16 133 cases of MI and 10 509 cases of IS occurred. The annual IRs of MI were 47.3 and 31.4 per 100 000 PY for individuals with and without mental disorders, respectively. The annual IRs of IS were 29.5 and 20.6 per 100 000 PY, respectively.

Regarding the risk of MI, patients with depressive disorder (IR 54.0 vs. 32.9 per 100 000 PY), bipolar disorder (IR 80.0 vs. 33.4 per 100 000 PY), schizophrenia (IR 94.8 vs. 33.4 per 100 000 PY), insomnia (IR 55.8 vs. 32.8 per 100 000 PY), anxiety disorder (IR 47.8 vs. 32.5 per 100 000 PY), post-traumatic stress disorder (IR 92.4 vs. 33.4 per 100 000 PY), personality disorder (IR 75.4 vs. 33.4 per 100 000 PY), somatoform disorder (IR 46.9 vs. 32.9 per 100 000 PY), eating disorder (49.8 vs. 33.4 per 100 000 PY), and substance use disorder (IR 104.8 vs. 33.2 per 100 000 PY) showed significantly higher risks of MI compared with those without any mental disorders (log-rank $P < 0.0001$ for each mental disorder except log-rank $P = 0.033$ for eating disorder, *Figure 2*). Similar findings were observed for IS. Patients with depressive disorder (IR 30.3 vs. 20.8 per 100 000 PY), bipolar disorder (IR 58.4 vs. 21.7 per 100 000 PY), schizophrenia (IR 70.1 vs. 21.7 per 100 000 PY), insomnia (IR 32.5 vs. 21.5 per 100 000 PY), anxiety disorder (IR 29.6 vs. 21.3 per 100 000 PY), personality disorder (IR 65.3 vs. 21.7 per 100 000 PY), somatoform disorder (IR 27.0 vs. 21.6 per 100 000 PY), and substance use disorder (IR 69.4 vs. 21.6 per 100 000 PY) had higher risks of IS compared with those without mental disorders (log-rank $P < 0.0001$, respectively, *Figure 3*). However, statistical significance was not observed in patients with post-traumatic stress disorder (IR 36.9 vs. 21.8 per 100 000 PY, log-rank $P = 0.119$) or those with eating disorder (IR 20.3 vs. 21.8 per 100 000 PY, log-rank $P = 0.828$).

Table 2 shows the unadjusted and adjusted Cox regression analyses for MI and IS according to the diagnosis of mental disorders. Patients with mental disorders showed significantly increased risks of MI (HR 1.58, 95% CI 1.51–1.64) and IS (HR 1.42, 95% CI 1.35–1.50) after adjusting for the covariates. For each mental disorder, young patients with mental disorders showed increased risks of MI with depressive disorders (HR 1.72, 95% CI 1.59–1.83), bipolar disorder (HR 2.40, 95% CI 1.86–3.10), schizophrenia (HR 2.61, 95% CI 1.98–3.44), insomnia (HR 1.73, 95% CI 1.61–1.87), anxiety disorder (HR 1.53, 95% CI 1.45–1.62), post-traumatic stress disorder (HR 3.13, 95% CI 2.02–4.85), personality disorder (HR 2.29, 95% CI 1.60–3.27), somatoform disorder (HR 1.49, 95% CI 1.39–1.60), eating disorder (HR 1.97, 95% CI 1.35–2.88), and substance use disorder (HR 2.47, 95% CI 2.13–2.87). Similarly, higher IS risks were observed in young patients with depressive disorder (HR 1.60, 95% CI 1.45–1.76), bipolar disorder (HR 2.64, 95% CI 1.96–3.55), schizophrenia (HR 2.95, 95% CI 2.13–4.07), insomnia (HR 1.45, 95% CI 1.32–1.61), anxiety disorder (HR 1.38, 95% CI 1.29–1.48), personality disorder (HR 3.06, 95% CI 2.08–4.50), somatoform disorder (HR 1.25, 95% CI 1.14–1.37), and substance use disorder (HR 2.44, 95% CI 2.03–2.93), but not in those with post-traumatic stress disorder (HR 1.86, 95% CI 0.93–3.72) and eating disorder (HR 1.17, 95% CI 0.65–2.12).

Subgroup analysis according to age and sex

To determine whether the prognostic association between mental disorders and cardiovascular diseases in young individuals is modified by age and sex, we performed a subgroup analysis (*Figure 4* and Supplementary material online, *Table 12*).

When participants were further stratified into those aged 20–29 years ($n = 2\,767\,097$) and those aged 30–39 years ($n = 3\,790\,630$), significant interactions between age and mental disorders for MI risks were shown. Patients aged 20 years with depressive disorder (*P* for interaction = 0.005), schizophrenia (*P* for interaction <0.001), anxiety disorder (*P* for interaction <0.001), and personality disorder (*P* for interaction < 0.001) showed more risk increments than did those aged 30–39 years with these mental disorders. No significant interactions were observed between additional age stratification and MI risk in patients with bipolar disorder, insomnia, post-traumatic stress

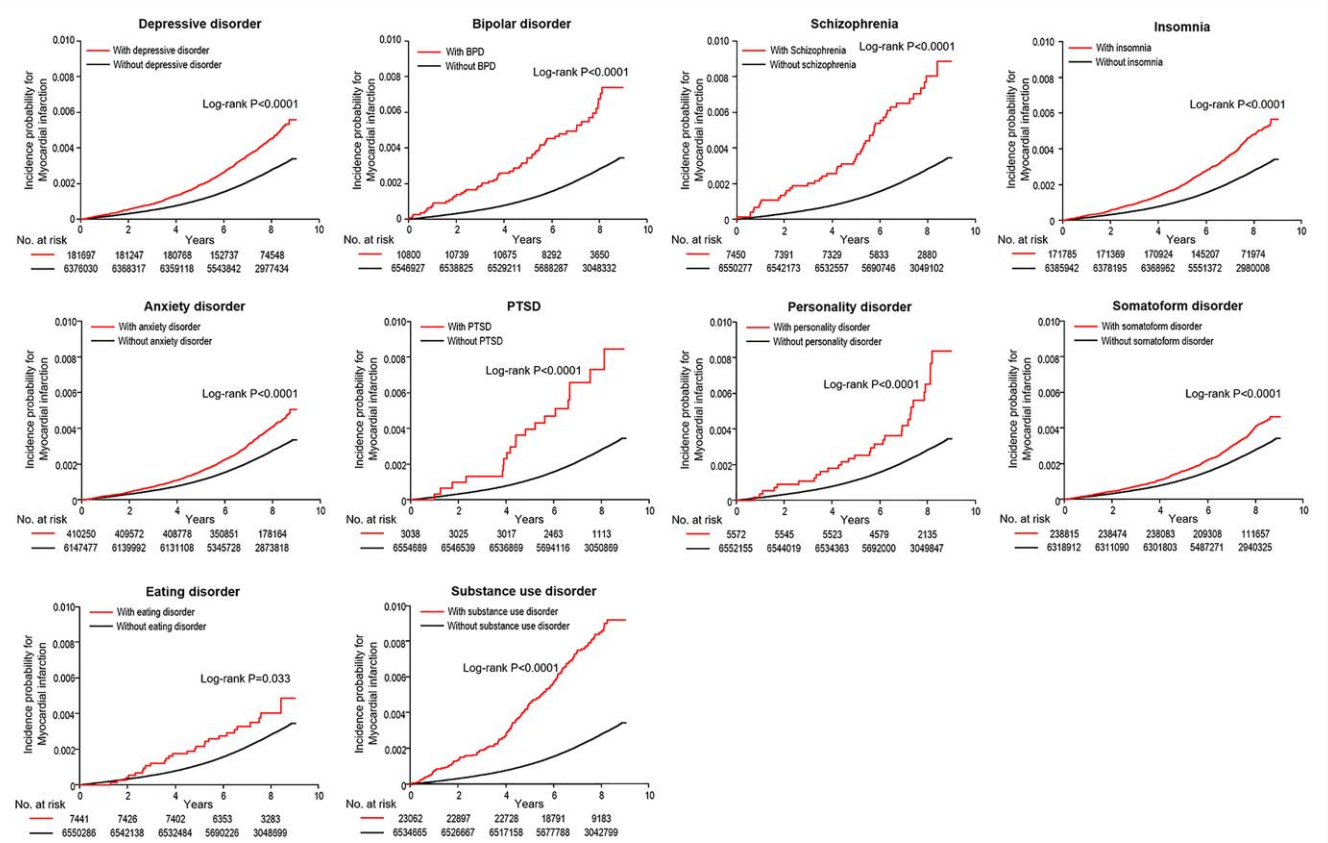


Figure 2 Excessive myocardial infarction risks according to the presence of mental disorders. Kaplan–Meier survival analyses were performed to evaluate the prognostic impact on myocardial infarction according to the presence of depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. BPD, bipolar disorder; PTSD, post-traumatic stress disorder.

disorder, somatoform disorder, eating disorder, and substance use disorder. In contrast, there was no significant interaction between age and mental disorders for IS risks except between age and post-traumatic stress disorder (*Figure 4A*).

Figure 4B shows the association between MI, IS, and mental disorders according to sex. Several mental disorders increased the relative risks of MI more in women than in men (P for interaction <0.001 for depressive disorder; P for interaction <0.001 for insomnia; P for interaction <0.001 for anxiety disorder; P for interaction = 0.040 for post-traumatic stress disorder; P for interaction = 0.019 for somatoform disorder; P for interaction = 0.012 for eating disorder; and P for interaction = 0.007 for substance use disorder) and IS (P for interaction <0.001 for depressive disorder and P for interaction = 0.004 for insomnia). In contrast, eating disorders decreased relative risks of IS more in women than in men (P for interaction = 0.013).

Discussion

In this study, we investigated the association between mental disorders and cardiovascular events of MI and IS in young persons. The principal findings of our study are summarized as follows: (i) a substantial number of young subjects aged 20–39 years (13.1%) were diagnosed with mental disorders; (ii) excessive risks of incident MI and IS were observed in patients with mental disorders including depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder; (iii) significant interactions were observed between age subgroups and mental disorders for MI risk, while no interactions were observed between age subgroups for IS risk except post-traumatic stress disorder; and (iv) depression and insomnia increased the relative risks of both MI and IS more in women than in men.

Patients with mental disorders have a shorter life expectancy than the general population.[1–4] Those with schizophrenia or bipolar disorder, which are often classified as severe mental disorders, demonstrate an even shorter life expectancy of 15–20 years.[1] Although patients with substance abuse and dependence showed increased risks of mortality,[25,26] unnatural deaths by suicide or drug abuse explain only a minor proportion of excessive mortality.[4,5,25] One previous study verified that around 70% of deaths in those with mental disorders were due to physical diseases.[25] Importantly, cardiovascular diseases reportedly contribute to approximately 20% or more of life-years lost in patients with mental disorders.[14,27] Accordingly, there were major concerns whether the presence of mental disorders might raise cardiovascular risks[28]; if patients with mental disorders have higher risks of cardiovascular diseases, especially in young persons, prevention and surveillance of cardiovascular diseases among these young patients during their lifetime should be considered. There are suggestions that taking mental disorders into account might improve cardiovascular risks stratification.[29,30]

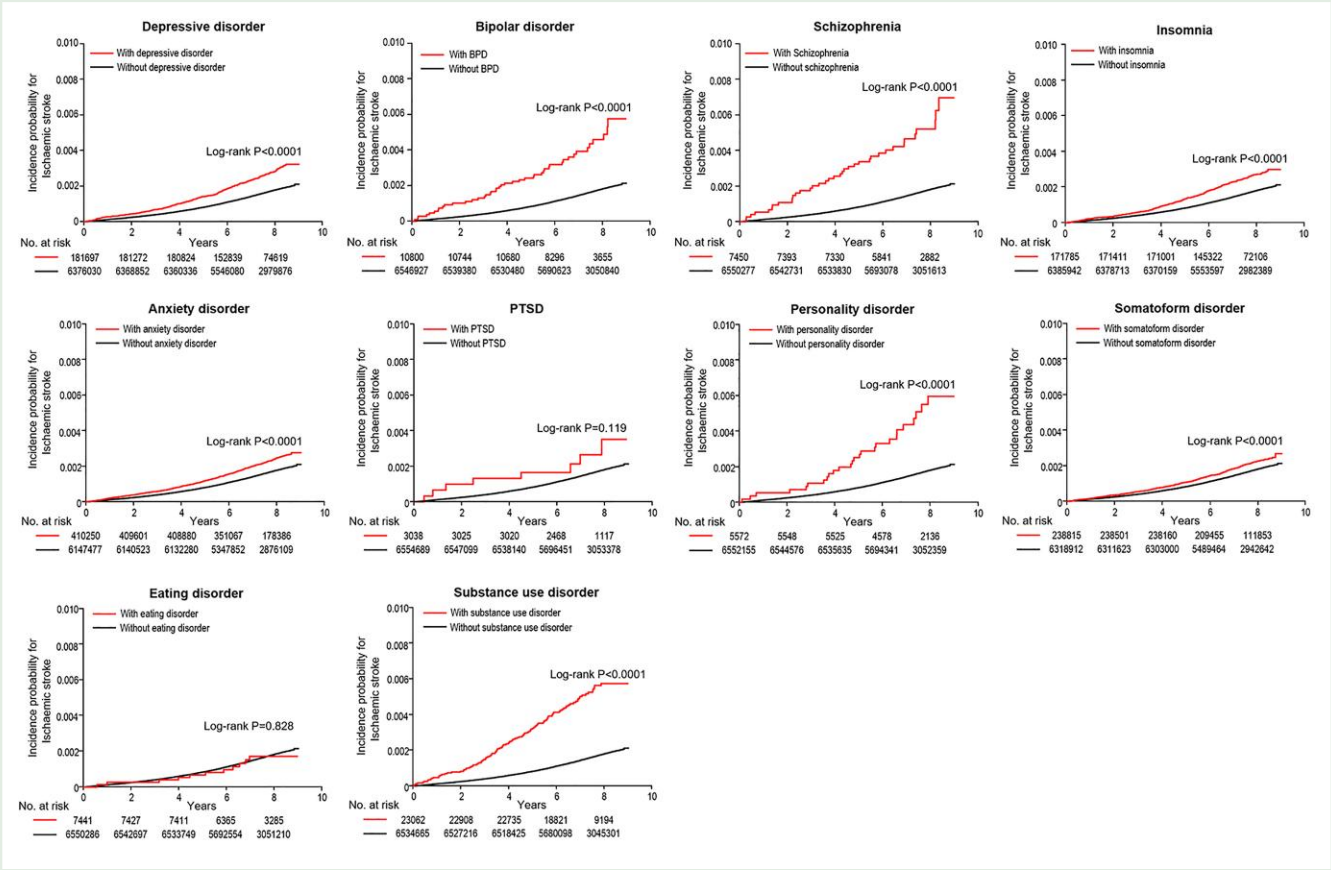


Figure 3 Excessive ischaemic stroke risks according to the presence of mental disorders. Kaplan–Meier survival analyses were performed to evaluate the prognostic impact on ischaemic stroke according to the presence of depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. BPD, bipolar disorder; PTSD, post-traumatic stress disorder.

Several putative explanations could be suggested for the association between mental disorders and an increased risk of cardiovascular disease. Patients with mental disorders are known to have increased oxidative stress markers as shown in both a meta-analysis[31] and prospective studies.[32,33] Autonomic nervous system dysfunction is commonly observed in adolescents and adults with mental disorders.[34] In addition, patients with mental disorders have higher levels of inflammatory markers than do those without mental disorders.[35] Considering that increased oxidative stress, impaired autonomic regulation, and overactivated inflammation contribute to endothelial dysfunction and accelerated atherosclerosis,[15] mental disorders are likely to raise the incidence of early cardiovascular diseases. Although some studies have suggested unfavourable lifestyle behaviours and poor cardiometabolic profiles in patients with mental disorders as a plausible linking mechanism between mental disorders and increased cardiovascular risks,[5,36] young patients with mental disorders did not show worse baseline characteristics in this nationwide study.

There were significant interactions between sex and mental disorders for risks of MI and IS. The relationship between cardiovascular disease and mental disorders in female persons has been overlooked and understudied compared with that in male persons.[37] Notably, only limited data in the literature are available for sex differences in the interactions between cardiovascular disease and mental disorders. For example, Vaccarino *et al.*[38] showed that psychological stress might lead to more microvascular endothelial dysfunction in female patients than in male patients. Interestingly, eating disorder increased relative risks of MI more in women than in men, while it decreased relative risks of IS more in women than in men. Considering these together, mechanistic studies on the interactions between sex differences, mental disorders, and cardiovascular diseases are needed.

Strengths and limitations

This study has two strengths. First, it was based on data from a nationwide prospective database managed by the Korean government. Patients with mental disorders are considered vulnerable for clinical studies. Therefore, a well-designed observational study is an optimal alternative that can provide valuable information. Second, we found that young patients with mental disorders had significantly increased risks of MI and IS despite similar baseline characteristics compared with those without. Considering our reports and recent studies which investigated the association between physical disorders and mental disorders,[39,40] further studies should analyse the preventive benefits of proper management of mental disorders and surveillance of cardiovascular diseases in young patients with mental disorders.

This study also has few limitations. First, the study results were derived from patients with depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorder, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. Thus, the results of the present study cannot be generalized to other mental disorders. Second, we did not analyse data regarding medications that were prescribed to the patients for

Table 2 Increased risks of myocardial infarction and stroke in patients with mental disorders

Mental disorders		Number	Events	Follow-up duration	Incidence rates[a]	Hazard ratio (95% confidence interval)[b]	
						Model 1	Model 2
Myocardial infarction							
Mental disorders	No	5 700 800	13 176	41 993 717	31.4	1 (reference)	1 (reference)
	Yes	856 927	2957	6 253 073	47.3	1.52 (1.46–1.58)	1.58 (1.51–1.64)
Depressive disorder	No	6 376 030	15 425	46 934 737	32.9	1 (reference)	1 (reference)
	Yes	181 697	708	1 312 053	54.0	1.67 (1.55–1.80)	1.72 (1.59–1.83)
Bipolar disorder	No	6 546 927	16 073	48 171 506	33.4	1 (reference)	1 (reference)
	Yes	10 800	60	75 284	79.7	2.49 (1.93–3.21)	2.40 (1.86–3.10)
Schizophrenia	No	6 550 277	16 083	48 194 057	33.4	1 (reference)	1 (reference)
	Yes	7450	50	52 734	94.8	2.92 (2.21–3.85)	2.61 (1.98–3.44)
Insomnia	No	6 385 942	15 439	47 003 801	32.9	1 (reference)	1 (reference)
	Yes	171 785	694	1 242 990	55.8	1.72 (1.60–1.86)	1.73 (1.61–1.87)
Anxiety disorder	No	6 147 477	14 704	45 257 118	32.5	1 (reference)	1 (reference)
	Yes	410 250	1429	2 989 672	47.8	1.48 (1.41–1.57)	1.53 (1.45–1.62)
Post-traumatic stress disorder	No	6 554 689	16 113	48 225 143	33.4	1 (reference)	1 (reference)
	Yes	3038	20	21 647	92.4	2.84 (1.83–4.40)	3.13 (2.02–4.85)
Personality disorder	No	6 552 155	16 103	48 206 997	33.4	1 (reference)	1 (reference)
	Yes	5572	30	39 793	75.4	2.32 (1.62–3.32)	2.29 (1.60–3.27)
Somatoform disorder	No	6 318 912	15 306	46 484 150	32.9	1 (reference)	1 (reference)
	Yes	238 815	827	1 762 640	46.9	1.42 (1.33–1.53)	1.49 (1.39–1.60)
Eating disorder	No	6 550 286	16 106	48 192 615	33.4	1 (reference)	1 (reference)
	Yes	7441	27	54 175	49.8	1.51 (1.04–2.20)	1.97 (1.35–2.88)
Substance use disorder	No	6 534 665	15 961	48 082 627	33.2	1 (reference)	1 (reference)
	Yes	23 062	172	164 163	104.8	3.23 (2.78–3.75)	2.47 (2.13–2.87)
Ischaemic stroke							
Mental disorders	No	5 700 800	8664	42 003 329	20.6	1 (reference)	1 (reference)
	Yes	856 927	1845	6 255 229	29.5	1.44 (1.37–1.51)	1.42 (1.35–1.50)
Depressive disorder	No	6 376 030	10 053	46 946 026	21.4	1 (reference)	1 (reference)
	Yes	181 697	456	1 312 532	34.7	1.64 (1.49–1.80)	1.60 (1.45–1.76)
Bipolar disorder	No	6 546 927	10 465	48 183 237	21.7	1 (reference)	1 (reference)
	Yes	10 800	44	75 321	58.4	2.77 (2.06–3.72)	2.64 (1.96–3.55)
Schizophrenia	No	6 550 277	10 472	48 205 807	21.7	1 (reference)	1 (reference)
	Yes	7450	37	52 751	70.1	3.30 (2.39–4.55)	2.95 (2.13–4.07)
Insomnia	No	6 385 942	10 105	47 014 922	21.5	1 (reference)	1 (reference)
	Yes	171 785	404	1 243 637	32.5	1.53 (1.38–1.69)	1.45 (1.32–1.61)
Anxiety disorder	No	6 147 477	9623	45 267 896	21.3	1 (reference)	1 (reference)
	Yes	410 250	886	2 990 663	29.6	1.40 (1.31–1.50)	1.38 (1.29–1.48)
Post-traumatic stress disorder	No	6 554 689	10 501	48 236 890	21.9	1 (reference)	1 (reference)
	Yes	3038	8	21 668	36.9	1.73 (0.86–3.45)	1.86 (0.93–3.72)
Personality disorder	No	6 552 155	10 483	48 218 758	21.7	1 (reference)	1 (reference)
	Yes	5572	26	39 800	65.3	3.05 (2.08–4.49)	3.06 (2.08–4.50)
Somatoform disorder	No	6 318 912	10 032	46 495.200	21.6	1 (reference)	1 (reference)
	Yes	238 815	477	1 763 359	27.1	1.25 (1.14–1.37)	1.25 (1.14–1.37)
Eating disorder	No	6 550 286	10 498	48 204 342	21.8	1 (reference)	1 (reference)
	Yes	7441	11	54 216	20.3	0.94 (0.52–1.69)	1.17 (0.65–2.12)
Substance use disorder	No	6 534 665	10 395	48 094 271	21.6	1 (reference)	1 (reference)
	Yes	23 062	114	164 288	69.4	3.26 (2.71–3.92)	2.44 (2.03–2.93)

[a]Annual event incidence rates were calculated per 100 000 patient-years from the baseline population.
[b]Model 1 for univariate analyses; Model 2 for adjusted age, sex, hypertension, diabetes mellitus, dyslipidaemia, metabolic syndrome, chronic kidney disease, current smoking, heavy alcohol consumption, regular physical activity, and low-income level.

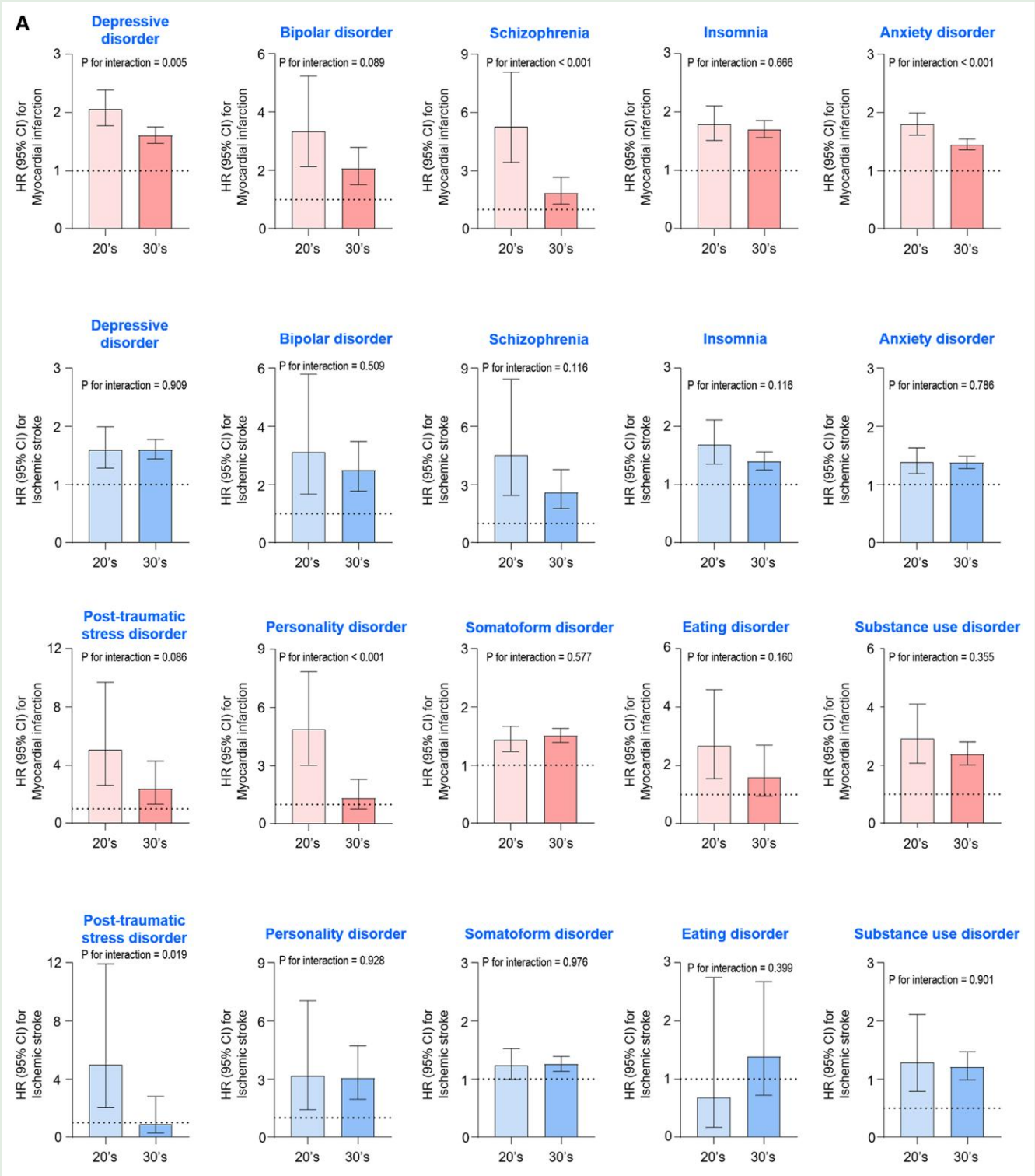


Figure 4 Association between myocardial infarction, ischaemic stroke, and mental disorders according to age and sex. After stratifying patients into subgroups according to age and sex—patients aged 20–29 years and 30–39 years (*A*) and patients with male or female sex (*B*)—the risks for myocardial infarction and ischaemic stroke associated with baseline mental disorder are shown. HRs with 95% CIs are presented as dot and whisker plots after adjusting for covariates. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidaemia, metabolic syndrome, chronic kidney disease, current smoking, heavy alcohol consumption, regular physical activity, and low-income level. CI, confidence interval; HR, hazard ratio.

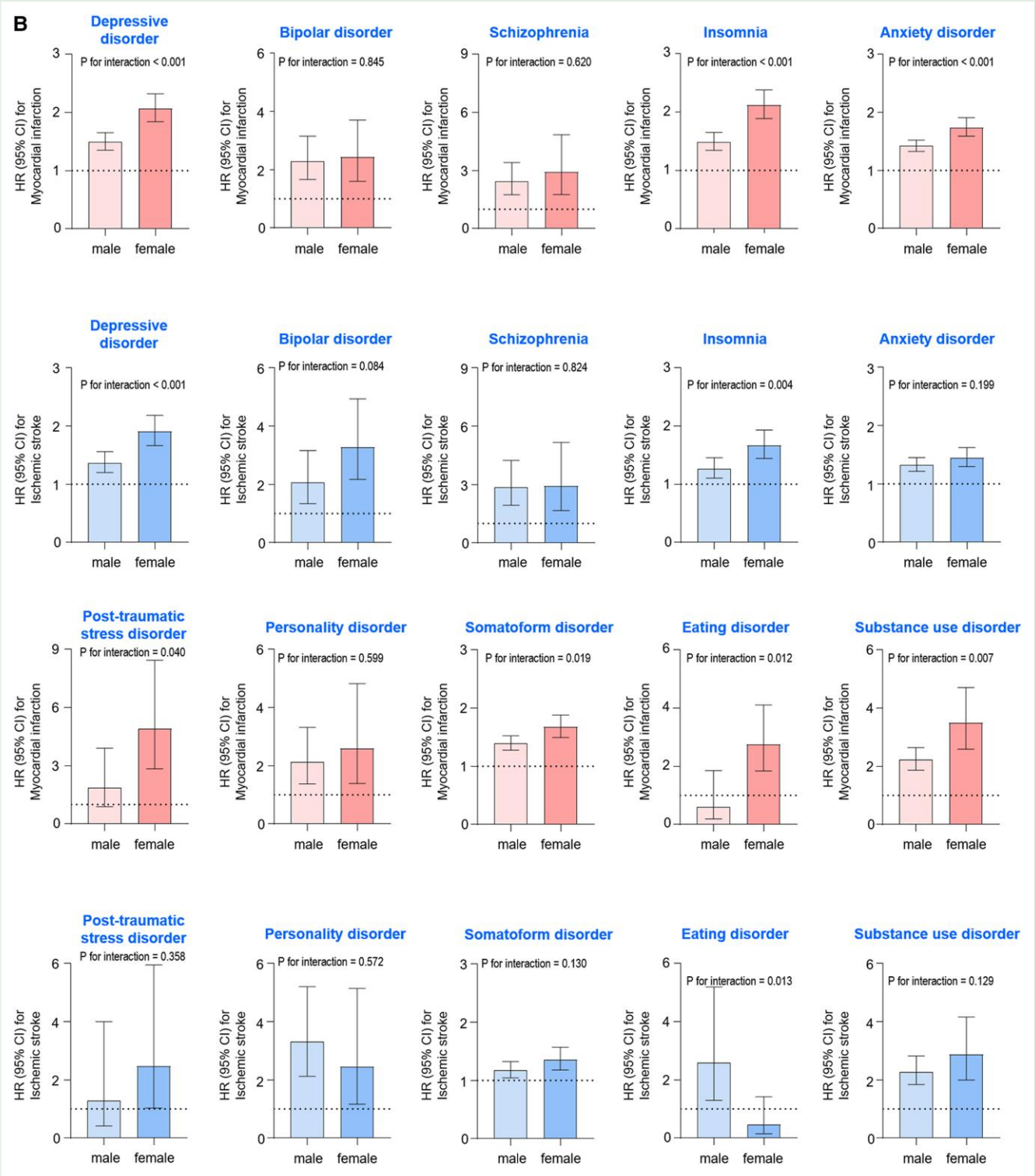


Figure 4 Continued

their mental disorders. Considering that some medications that are used to treat mental disorders influence metabolic profiles, they may serve as a confounding factor. There is also a study that the persistent use of psychostimulants could result in progressive cardiovascular pathology.[41] Further studies are demanded to verify mediating effects of drugs for an association between mental disorders and cardiovascular outcomes, and authors are undergoing a study to see if the prognosis of young patients with mental disorders differs depending on whether the patients are being treated or not and which classes of medications are being demanded. Third, clinical endpoints defined as fatal MI, fatal IS,

all-cause mortality, and cause of deaths might provide additional clinical information in addition to MI and IS, information of which is not available. Further, there could be selection biases in undergoing general health examination, although more than three-quarters of adults aged between 20 and 39 years were attended. However, this nationwide cohort provided a notably large number of subjects with long-term follow-up, effectively reflecting real-world clinical practice.

Conclusions

Mental disorders in young patients may have deleterious effects on the incidence of both MI and IS events. This is evident in mental disorders including depressive disorder, bipolar disorder, schizophrenia, insomnia, anxiety disorders, post-traumatic stress disorder, personality disorder, somatoform disorder, eating disorder, and substance use disorder. There were significant interactions between age and mental disorders and between sex and mental disorders for risks of MI and IS. Cardiovascular disease prevention efforts are needed to prevent MI and IS in young patients with mental disorders.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

C.S.P. contributed to the conception and design of the work, data interpretation and analysis, and drafting of the manuscript. E.-K.C. contributed to conception, design, data acquisition and interpretation, and critical revision of the manuscript. K.-D.H. contributed to the data acquisition and analysis. H.-J.A., S.K., S.-R.L., S.O., and G.Y.H.L. contributed to the conception and design of the work and critically revised the manuscript. E.-K.C. acts as guarantor for the paper.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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