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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Risk of incident mental disorders in hypertrophic cardiomyopathy: a nationwide propensity-matched study

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Aims We sought to determine the risk of mental disorders in patients with hypertrophic cardiomyopathy (HCM) compared with those without HCM.

Methods and results This is a retrospective propensity score-matched cohort study using nationwide population-based data from the Korean National Health Insurance Service. Overall, 4046 patients with HCM and 12138 matched individuals were followed up until the first diagnosis of mental disorders or the end of the follow up. The primary outcome was a composite of incident mood, anxiety, stress-related, or somatoform disorders. Secondary outcomes included two components of the primary outcome (i.e. mood disorders and anxiety/stress-related/somatoform disorders). During a median follow-up period of 4.1 years, the incidence rate of the primary outcome was 54.4 and 31.5/1000 person-years among the HCM and control groups, respectively, resulting in a hazard ratio (HR) of 1.719 (95% confidence interval: 1.589–1.860). Within the first month after HCM diagnosis, the HR for the primary outcome was 3.074 (2.096–4.508). Beyond 1 month, the HRs decreased, ranging from 2.281 (1.952–2.665) during 1–12 months, to 2.087 (1.831–2.380) during 12–36 months and 1.258 (1.090–1.452) after 36 months of follow up. Similar results were observed for the secondary outcomes. In sensitivity analysis, the risk of the specific categories of mental disorders, including single or recurrent depressive episodes and anxiety disorders, was also higher in patients with HCM than matched controls.

Conclusion HCM was significantly associated with the risk of incident mental disorders, particularly within 1 year after HCM diagnosis, underscoring the importance of screening mental health problems, including mood and anxiety disorders, in patients with HCM.

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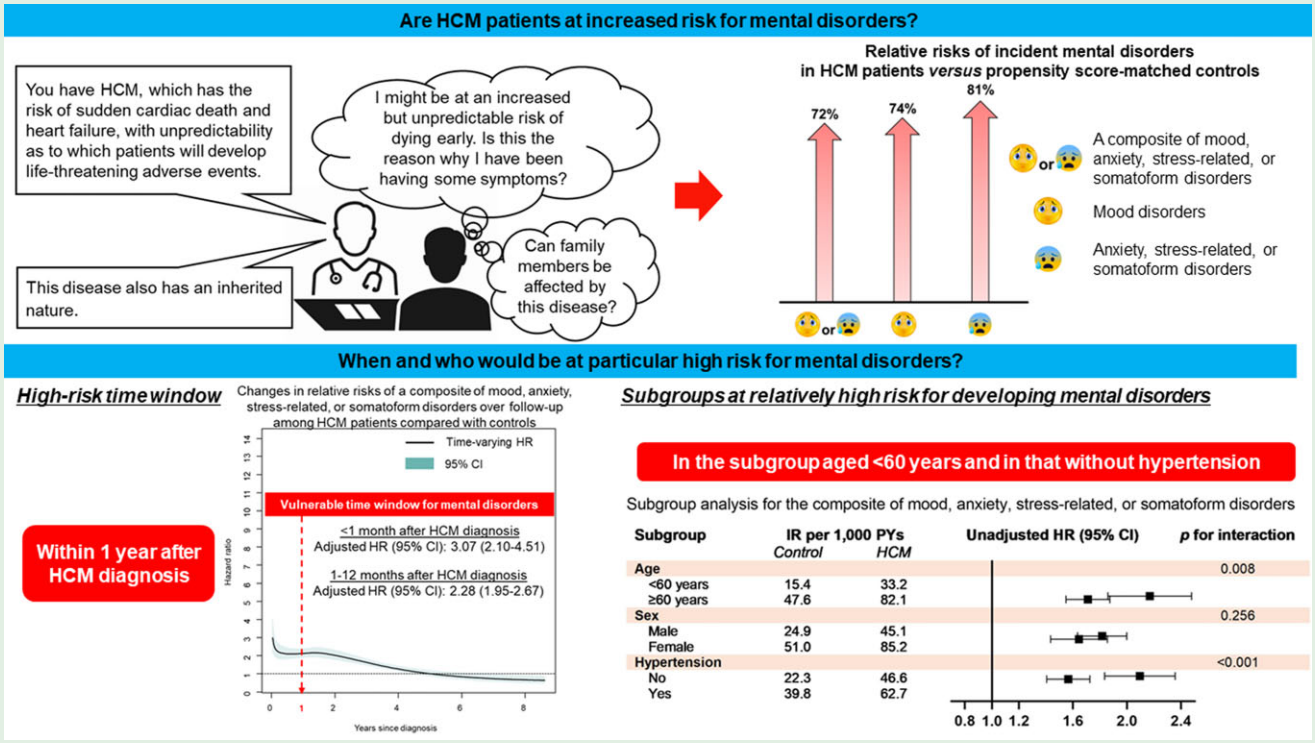
Graphical Abstract



Keywords Hypertrophic cardiomyopathy • Mental disorders • High-risk time window

Introduction

Recent advances in cardiovascular interventions have lowered annual mortality rates to <1.0% in patients with hypertrophic cardiomyopathy (HCM), leading to a near-normal life expectancy.[1] However, ~30–40% of patients with HCM experience cardiac complications pertinent to the pathophysiology of HCM, including arrhythmias, myocardial ischaemia, and heart failure (HF).[1,2] Thus, contemporary guidelines recommend that these patients should undergo a comprehensive clinical evaluation, focusing on the presence of such abnormalities and their impact on disease management.[1]

Patients with HCM may also experience multiple non-cardiac comorbidities,[1] which can potentially complicate management and prognosis. However, the role of non-cardiac morbidities is less well understood in patients with HCM than in patients with other cardiovascular diseases (CVDs). Furthermore, among non-cardiac comorbidities, the available data are extremely limited on mental health issues, whose importance has been increasingly recognized as a modifiable prognostic factor for CVDs.[3] Among different types of mental disorders, the most widely studied mental disorders associated with CVDs are non-psychotic disorders, including mood,[4,5] anxiety,[5,6] stress-related,[7] and somatoform disorders,[8,9] which are also far more common than psychotic disorder.[10,11] These mental disorders may be substantially prevalent in patients with HCM considering that they are generally informed of the risks of sudden cardiac death (SCD) and HF, with great unpredictability as to which patients will develop life-threatening adverse events. Indeed, illness perception can affect heart-focused anxiety in patients with HCM.[12] Similar to other inherited heart diseases,[13,14] the inherited nature of HCM can also cause psychological distress. Furthermore, after the diagnosis of HCM, most patients adjust their daily lifestyle and intentionally reduce their physical activity at work and leisure time,[15,16] which in turn may reduce emotional well-being and increase the risk of mental disorders, including mood, anxiety, stress-related, and somatoform disorders.[16,17] The experience of subjective symptoms, including dyspnoea, dizziness, chest pain, and palpitations, could also lead to negative emotional impacts, such as feeling anxious or depressed.[18,19] On the other hand, given that non-psychotic mental disorders are associated with higher mortality, lower quality of life, excessive disability, and increased healthcare expenditure in patients with CVD,[5,20] these disorders may also result in adverse consequences for medical care of HCM. Indeed, depression and anxiety are reported to increase the risk of HF and SCD in patients with HCM.[21,22] Stress-related disorders are robustly associated with the risk of various cardiovascular events, such as HF, arrhythmia, emboli/thrombosis,[7] which are important complications in the clinical course of HCM. Somatoform disorders can lead to functional impairment and lowered quality of life for patients with HCM.[8]

Considering the possible high comorbidity with non-psychotic mental disorders in patients with HCM and their detrimental impacts on HCM prognosis, proper screening and management of these mental health problems are important. Screening for mental disorders in patients with CVDs may be clinically feasible and practical, because it has been suggested that healthcare providers can use simple screening measures to assess mental health status.[3] Moreover, appropriate interventions to improve mental health may have beneficial effects on cardiovascular health.[3] These findings support that implementing preventive screening and interventions can lead to better clinical outcomes in patients with CVDs than contemporary approaches focusing on the specific physical condition. However, no information is available even on the incidence of mental disorders, including depression and anxiety, in patients with HCM. In this regard, investigating the risk of incident mental disorders in patients with HCM may be valuable in

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drawing attention to the importance of assessing and treating these neglected problems in this population, and in providing a basis for future studies. Furthermore, considering that the efficacy of preventive measures is dependent on providing intervention at the right time,[23] assessment of the time-dependent risk profile of mental disorders may have important clinical implications in guiding physicians for timely and targeted psychological interventions for patients with HCM.

Taking advantage of a large nationwide population data from Korea, we examined whether the risk of incident non-psychotic mental disorders is higher among patients with HCM compared with propensity-matched controls without HCM. In our study, mood, anxiety, stress-related, and somatoform disorders were included as the mental disorders of interest, based on the aforementioned rationales (i.e. the possible high incidence and substantial prognostic importance of these disorders). We also explored whether there is a time-dependent risk pattern for these mental disorders after the diagnosis of HCM.

Methods

Data source

This retrospective cohort study used the nationwide population-based claims database of the National Health Insurance Service (NHIS), which contains anonymized health-related information of ~97% Koreans, including demographics, medical history, lifestyle behaviours obtained from questionnaires, and laboratory testing.[24] The remaining 3% of individuals are those covered by the Medical Aid program for which entitlement criterion is earning <40% of median income. The average missing rate for the questionnaire was 0.22% from 2010 to 2016. Quality control of laboratory tests was conducted in accordance with the procedures of the Korean Association of Laboratory Quality Control.[24]

Study population

We evaluated the data of Korean adults aged ≥20 years who were diagnosed with HCM during 2010–16. HCM was confirmed if (i) individuals had at least one outpatient visit or admission claim with an International Classification of Disease-Tenth Revision-Clinical Modification (ICD-10-CM) code for HCM (42.1 or 42.2) and (ii) individuals were registered as having HCM in the rare intractable diseases (RID) programme, which strictly controls the approval and registration of the HCM diagnostic code on the basis of imaging information and review by qualified medical experts and health insurance claims professionals to ensure appropriate provision of insurance benefits provided by the Korean government. The accuracy of these codes used for HCM was previously validated by investigating the medical records and imaging of a random sample of 1100 individuals, with sensitivity, specificity, and accuracy of 91.5, 100, and 92.5%, respectively.[25] The first entry of the diagnosis code pertaining to HCM on outpatient or inpatient claims was taken as the date of diagnosis. Individuals without HCM served as control subjects and were selected via propensity-score matching. The study population was followed up until the first diagnosis of mental disorders or the end of the follow-up period (31 December 2018), whichever was earlier. The study design and timeline are presented in Supplementary material online, *Figure S1*.

Identification of mental disorders

Mental disorders were defined based on the following ICD-10-CM codes: Affective psychotic disorders (F25, F30–31, F32.3, F33.3); mood disorders without psychotic symptoms (F32–34, F38–39, excluding F32.3 and F33.3); and neurotic, stress-related, and somatoform disorders (F40–F48). During the follow-up period after HCM diagnosis, consecutive records of mental disorders twice or more with an interval of ≤12 months were regarded as incident mental disorders.[26,27] Detailed information on diagnostic codes used to identify mental disorders is provided in Supplementary material online, *Table S1*. The primary outcome was a composite of mood, anxiety, stress-related, and somatoform disorders. We used this composite outcome to avoid an arbitrary choice between several important outcomes and to address more than one aspect of the patient's mental health status. Secondary outcomes included two separate components of the primary outcome consisting of (i) mood disorders and (ii) anxiety/stress-related/somatoform disorders, which were used for analyses on individual outcomes.

Covariates

The NHIS provided data on household income in percentiles; the low-income level was defined as being in the bottom 20% of the income distribution. A questionnaire was used to obtain information regarding consumption of alcohol and cigarettes and physical activities. Regular physical activity was defined as any type of physical activity ≥5 times/week. Smoking status was classified based on self-report into three categories: never, former, or current. Details regarding the definition of data variables are provided in Supplementary material online, *Table S2*.

Statistical analysis

No formal sample size calculation was performed because of the observational nature of this study and the lack of previous specific studies on the topic. Descriptive statistics are presented as mean ± standard deviation or medians (with interquartile ranges) for continuous variables and numbers (percentages) for categorical variables. For comparisons between groups, we used unpaired Student's *t*-test for continuous variables and the χ^2 or Fisher's exact test for categorical variables, as appropriate. Considering that data from cohort study can be analysed using incidence rate, we used incident rates as measures of comparative effect in this study. The incidence rate was calculated as events per 1000 person-years of follow up, and the person-years at risk of mental disorders was counted from the day of the diagnosis of HCM to the date of the diagnosis of mental disorders, or 31 December 2018, whichever came first. The chronological trend of outcomes was expressed as Kaplan–Meier estimates and compared by log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using Cox proportional hazards models to estimate associations between HCM and outcomes. To match two groups, we applied propensity score matching to control for sampling bias, which is a widely used method to reduce confounding due to measured covariates in observational studies.[28,29] Propensity score was calculated for each individual using logistic regression for HCM, adjusting for covariates measured at baseline (*Table 1*). We selected these variables to calculate propensity scores based on the previous studies suggesting their associations with the risk of mental disorders.[3,30] Each patient with HCM was then matched to three non-HCM controls with a calliper for nearest-neighbour matching within the first 4–8 digits. To examine matching effectiveness, we computed absolute standardized differences (ASDs), whose values <10% and closer to zero, demonstrate a more balanced cohort. Since three controls per one HCM case were individually matched per propensity score, we used the date of diagnosis as the index date for both individuals.

To assess changes in the relative risk of mental disorders over the follow-up period in patients with HCM vs. matched controls, we visualized the time-dependent associations of HCM with the risk of mental disorders using flexible parametric survival models.[7] Considering the substantially elevated risk of mental disorders immediately after HCM diagnosis, we examined associations separately during the first month after diagnosis and beyond this period (<1 month, 1–12 months, 1–3 years, or >3 years of follow up) using HRs and 95% CIs derived from conditional Cox regression models. The time since the index date was used as the underlying time scale.

In sensitivity analysis, (i) single or recurrent depressive episodes (depressive episode [F32 excluding F32.3] and recurrent depressive disorder [F33 excluding F33.3]) and (ii) anxiety disorders (phobic anxiety disorders [F40] and other anxiety disorders [F41]) were used as outcomes to allow comparison with previous studies in which these variables were predominantly adopted as outcomes, and also to better inform the specific mental disorders that patients with HCM might be at risk for developing. We performed another sensitivity analysis after excluding individuals diagnosed with mental disorders of interest within the first 1 year after HCM diagnosis (i.e. a 1-year lag) to account for induction and latent periods,[31] and to minimize the problem of possible inclusion of individuals having mental disorders at baseline. Since the original matching was not preserved in these analyses, we adjusted for matching covariates. Prespecified subgroup analyses were performed according to age, sex, and hypertension, based on clinical relevance and previous studies.[1,32] Interaction tests for subgroup analyses

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Table 1 Baseline characteristics before and after matching

	Before matching			After matching		
Variable[a]	Control ($n = 52\,056$)	HCM ($n = 5089$)	ASD	Control ($n = 12\,138$)	HCM ($n = 4046$)	ASD
Age (years)	60.1 ± 12.3	59.4 ± 12.2	0.058	59.3 ± 13.0	59.0 ± 12.3	0.020
Male	36 318 (69.8)	3753 (73.8)	0.088	8921 (73.5)	2995 (74.0)	0.012
BMI (kg/m^2)	24.2 ± 3.1	25.3 ± 3.2	0.354	25.1 ± 3.3	25.1 ± 3.1	0.010
Smoking						
Never	26 981 (51.8)	2409 (47.3)	0.090	5783 (47.6)	1939 (47.9)	0.006
Former	12 438 (23.9)	1361 (26.7)	0.066	3204 (26.4)	1074 (26.5)	0.003
Current	12 637 (24.3)	1319 (25.9)	0.038	3151 (26.0)	1033 (25.5)	0.010
Alcohol consumption (g/day)						
0	27 491 (52.8)	2540 (49.9)	0.058	6019 (49.6)	1992 (49.2)	0.007
1–30	20 019 (38.5)	2073 (40.7)	0.046	4960 (40.9)	1678 (41.5)	0.012
>30	4546 (8.7)	476 (9.4)	0.022	1159 (9.6)	376 (9.3)	0.009
Regular physical activity	11 534 (22.2)	1118 (22.0)	0.005	2820 (23.2)	927 (22.9)	0.008
Low-income level	7232 (13.9)	738 (14.5)	0.017	1772 (14.6)	583 (14.4)	0.005
Hypertension	17 647 (33.9)	2704 (53.1)	0.395	6327 (52.1)	2009 (49.7)	0.050
Diabetes mellitus	6581 (12.6)	679 (13.3)	0.021	1812 (14.9)	542 (13.4)	0.044
Dyslipidaemia	11 031 (21.2)	1947 (38.3)	0.380	4436 (36.6)	1394 (34.5)	0.044
Ischaemic heart disease	4059 (7.8)	2346 (46.1)	0.957	4651 (38.3)	1467 (36.3)	0.043
Heart failure	928 (1.8)	882 (17.3)	0.548	1167 (9.6)	428 (10.6)	0.032
Atrial fibrillation	606 (1.2)	621 (12.2)	0.453	720 (5.9)	324 (8.0)	0.082
COPD	3910 (7.5)	621 (12.2)	0.158	1656 (13.6)	518 (12.8)	0.025
Medications						
ACEI	1199 (2.3)	448 (8.8)	0.287	908 (7.5)	312 (7.7)	0.009
ARB	12 011 (23.1)	2023 (39.8)	0.365	4794 (39.5)	1517 (37.5)	0.041
CCB	9277 (17.8)	1138 (22.4)	0.113	3130 (25.8)	973 (24.1)	0.040
Beta-blocker	4782 (9.2)	2457 (48.3)	0.958	4869 (40.1)	1549 (38.3)	0.038
Warfarin	301 (0.6)	319 (6.3)	0.317	342 (2.8)	165 (4.1)	0.069
NOAC	118 (0.2)	64 (1.3)	0.120	66 (0.5)	30 (0.7)	0.025
Laboratory tests						
Total cholesterol (mg/dL)	195.7 ± 39.55	192.1 ± 38.9	0.092	193.1 ± 44.7	193.6 ± 38.5	0.011
HDL-C (mg/dL)	53.1 ± 18.68	51.0 ± 15.6	0.124	51.5 ± 16.4	51.7 ± 16.3	0.010
LDL-C (mg/dL)	115.7 ± 58.27	113.8 ± 42.7	0.039	114.0 ± 50.8	114.6 ± 42.2	0.012
Triglyceride (mg/dL)	121.0 (120.4–121.5)	123.5 (121.7–125.3)	0.039	124.4 (123.2–125.5)	122.6 (120.6–124.7)	0.026
Glucose (mg/dL)	103.4 ± 27.1	103.1 ± 25.3	0.012	103.9 ± 25.9	103.0 ± 26.0	0.033
Haemoglobin (g/dL)	14.2 ± 1.6	14.6 ± 1.6	0.238	14.5 ± 1.6	14.6 ± 1.6	0.024
GFR (mL/min/1.73 m^2)	87.4 ± 49.1	82.4 ± 46.4	0.105	83.1 ± 36.9	82.3 ± 40.1	0.021

Values given as number (percentage), mean ± standard deviation, or median (interquartile range) unless otherwise indicated.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASD, absolute standardized difference; BMI, body mass index; CCB, calcium-channel blocker; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NOAC, non-vitamin K antagonist oral anticoagulant.
[a]All variables were used for the calculation of propensity scores.

for the primary outcome were performed by adding an interaction term between the prespecified subgroup and HCM diagnosis. Differences were considered statistically significant if two-sided *P*-values were <0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Ethics

This study complied with the Declaration of Helsinki and was exempt from review by the institutional review board of our institution (E-2005-026-1121) owing to the retrospective data collection from an anonymized database, allowing the maintenance of participants' confidentiality. The requirement for informed consent was waived.

Results

Baseline characteristics

Among the 13 239 individuals diagnosed with HCM during 2010–16, individuals previously diagnosed with mood disorders ($n = 928$) or anxiety/stress-related/somatoform disorders ($n = 1225$) before HCM diagnosis were excluded to reduce the chances of reverse causality. Individuals who had not undergone health check-ups within 2 years before HCM diagnosis ($n = 5933$) were excluded to minimize the possibility of including individuals with pre-existing mental disorders. Individuals with missing data for covariables ($n = 64$) were excluded, resulting in

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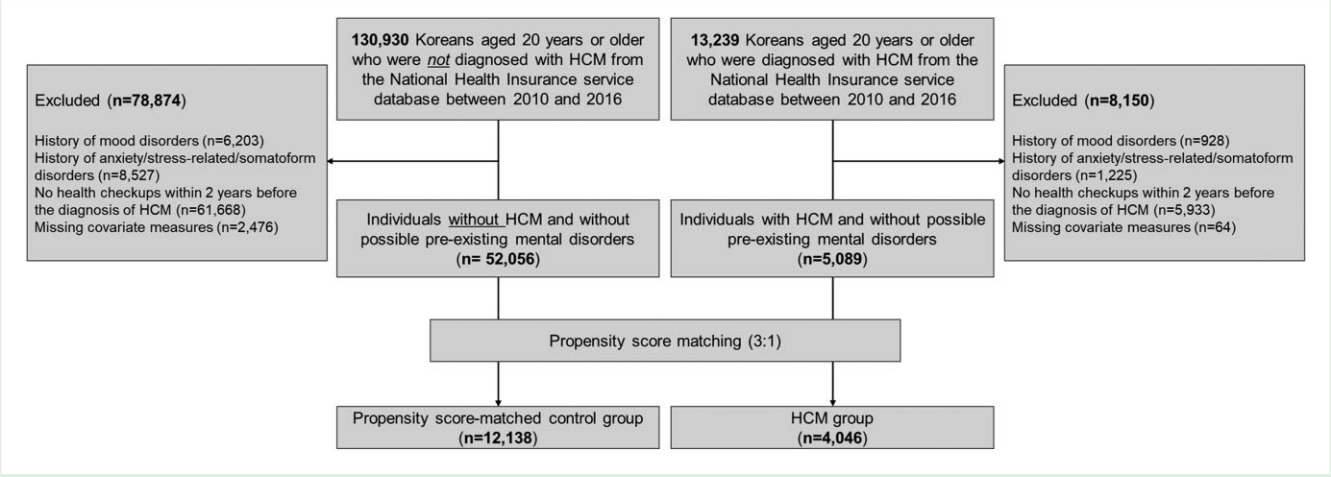

Figure 1 Flow diagram of the study population. HCM, hypertrophic cardiomyopathy.

5089 patients with HCM. During the propensity score-matching process on a 3:1 basis, 1043 patients with HCM were left unmatched and were not used in subsequent analyses. Therefore, there remained 4046 patients with HCM matched to 12 138 controls without HCM (a total of 16 184 individuals; *Figure 1*). The match was successful in achieving a relatively small imbalance across covariates, with ASD <10% for all baseline variables (*Table 1*). *Table 1* summarizes baseline characteristics of study population before and after matching. The comparison of the baseline characteristics between included and excluded patients with HCM is also presented in Supplementary material online, *Table S3*.

Association between HCM and mental disorders

Over a median 4.1-year follow-up period (interquartile range: 2.5–6.1 years), for the 4046 patients with HCM, there were 941 primary outcome events (incidence rate: 54.4/1000 person-years), including 474 patients diagnosed with mood disorders and 717 with anxiety/stress-related/somatoform disorders (*Table 2*). For the 12 138 controls, 1803 primary outcome events (incidence rate: 31.5/1000 person-years), including 860 diagnosed with mood disorders and 1275 with anxiety/stress-related/somatoform disorders, were reported during a median 4.6-year follow-up period (interquartile range: 3.0–6.5 years). The HR for the primary outcome was 1.719 (95% CI: 1.589–1.860) in patients with HCM. Risks of secondary outcomes were also significantly higher in patients with HCM than in controls, with the HR of 1.735 (1.551–1.941) for mood disorders and 1.813 (1.654–1.987) for anxiety/stress-related/somatoform disorders.

The Kaplan–Meier plots are shown in *Figure 2*. The risk of the primary outcome was significantly higher in patients with HCM than in controls, with curves showing early separation and continued divergence throughout the follow-up period (*Figure 2A*). When each outcome was examined separately, there was a gradual increase in the risk of mood disorders (*Figure 2B*) and an early increase in the risk of anxiety/stress-related/somatoform disorders (*Figure 2C*).

Time-varying risk of mental disorders after HCM diagnosis

Using flexible parametric models, we found a peak in the risk of the primary outcome followed by a rapid decline within 1 month after HCM diagnosis (see Supplementary material online, *Figure S2A*). Within the first month of follow up, the incidence rate of the primary outcome among patients with HCM was approximately three times that of their matched controls (164.0 vs. 52.2/1000 person-years), with an adjusted HR of 3.074 (2.096–4.508). The risks were attenuated but remained significant beyond 1 month of follow up (*Table 3*). The magnitude of relative risk gradually decreased thereafter, but the lower border of the 95% CI remained above an HR of 1 during ~4.5 years of follow up (see Supplementary material online, *Figure S2A*).

The association of HCM with secondary outcomes was greater with respect to the risk of mood disorders than anxiety/stress-related/somatoform disorders in the early [5.499 (2.432–12.430) vs. 2.617 (1.696–

Table 2 Risk of mental disorders associated with hypertrophic cardiomyopathy

		Event	PY	IR	HR (95% CI)	*P*-value
A composite of mood, anxiety, stress-related, and somatoform disorders	Control	1803	57 321	31.5	1 (reference)	<0.001
	HCM	941	17 283	54.4	1.719 (1.589–1.860)	
Mood disorders	Control	860	60 644	14.2	1 (reference)	<0.001
	HCM	474	19 318	24.5	1.735 (1.551–1.941)	
Anxiety/stress-related/somatoform disorders	Control	1275	58 490	21.8	1 (reference)	<0.001
	HCM	717	17 965	39.9	1.813 (1.654–1.987)	

CI, confidence interval; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; IR, incidence rate per 1000 person-years; PY, person-years.

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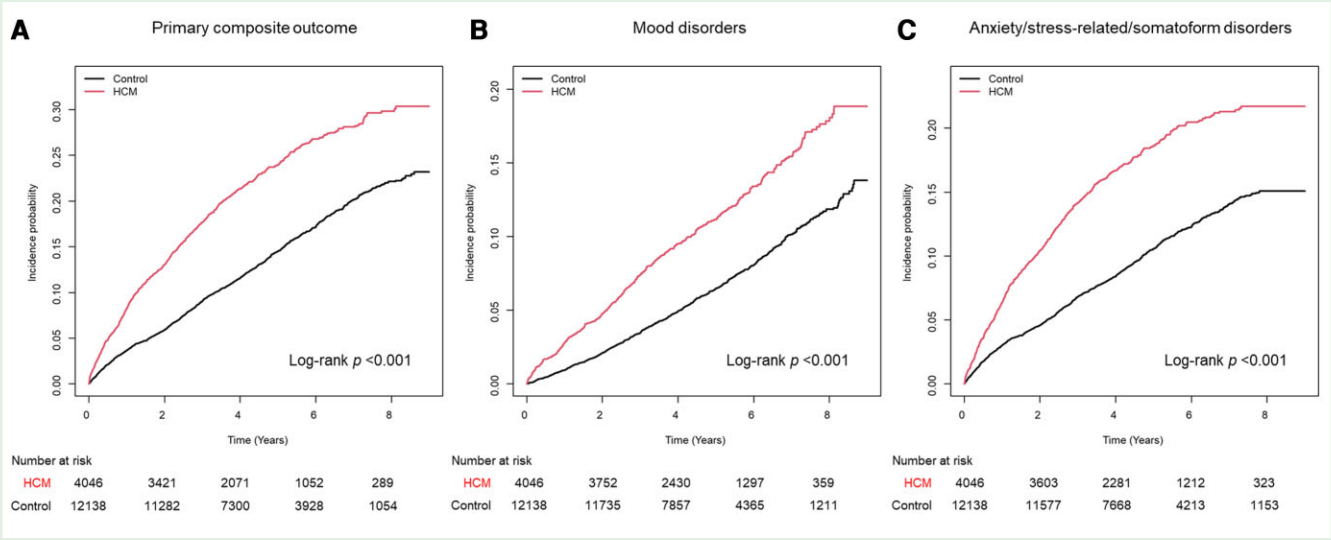

Figure 2 Kaplan–Meier plots for the risk of mental disorders in individuals with and without hypertrophic cardiomyopathy. Unadjusted Kaplan–Meier curves for the composite of mood, anxiety, stress-related, or somatoform disorders (*A*); mood disorders (*B*); and anxiety disorders/stress-related disorders/somatoform disorders (*C*) based on the presence or absence of hypertrophic cardiomyopathy. HCM, hypertrophic cardiomyopathy.

4.038)] and late phases of the follow-up period [1.300 (1.066–1.584) vs. 1.255 (1.045–1.506); *Table 3*]. The degree of early peak and rapid decline in the risk of mood disorders was greater than that of the primary outcome, but the increased risk continued to be significant >6.3 years after HCM diagnosis (see Supplementary material online, *Figure S2B*). The change in the risk of anxiety/stress-related/somatoform disorders was similar to that of the primary outcome (see Supplementary material online, *Figure S2C*).

Subgroup analyses

Subgroup analyses of prespecified variables, including age, sex, and hypertension, revealed that the risk of the primary outcome was higher in patients with HCM than in matched controls in all strata (see Supplementary material online, *Figure S3*). Significant modifications by age and presence of hypertension were observed (*P* for interaction = 0.008 and <0.001, respectively). The relative increased risk of the primary outcome associated with HCM was significantly greater in the subgroup aged <60 years [HR: 2.153 (95% CI: 1.866–2.485)] and in the subgroup without hypertension [2.084 (1.839–2.361)] than their counterparts [1.705 (1.550–1.875) for the subgroup aged ≥60 years; 1.559 (1.407–1.727) for the subgroup with hypertension], driven primarily by the particularly low baseline incidence rate of the primary outcome when the control subjects were <60 years or did not have hypertension.

Within 4046 patients with HCM, 620 (15.3%) and 390 (9.6%) were diagnosed as having HF and atrial fibrillation (AF), respectively, at the time of HCM diagnosis. The unadjusted risk of the primary outcome was significantly higher in patients with HCM with HF [1.295 (1.092–1.535)] or AF [1.454 (1.201–1.759)] than those without this comorbidity. However, after adjusting for covariates, the elevated risk was attenuated and became no longer significant, with an adjusted HR of 1.105 (0.918–1.331) for HF and 1.117 (0.843–1.482) for AF, respectively.

Sensitivity analyses

When sensitivity analysis was performed confining the study outcomes to the specific categories of mental disorders, including single or recurrent depressive episodes and anxiety disorders, the risks were significantly higher in patients with HCM than in controls, with an HR of 1.756 (1.566–1.970) for single or recurrent depressive episodes and 1.750 (1.591–1.926) for anxiety disorders (see Supplementary material online, *Table S4*). Further, we repeated all analyses after excluding individuals diagnosed with mental disorders within the first 1 year after HCM diagnosis. In these 1-year lag analyses, the relative risk elevations were attenuated, although they remained significant [1.638 (1.488–1.803) for the primary outcome, 1.619 (1.417–1.850) for mood disorders, 1.746 (1.556–1.959) for anxiety/stress-related/somatoform disorders; see Supplementary material online, *Figure S4* and Supplementary material online, *Table S5*].

Discussion

Principal findings

In this retrospective nationwide population-based and propensity score-matched study, we found that patients with HCM were at an elevated risk of the primary outcome (i.e. a composite of mood, anxiety, stress-related, and somatoform disorders). The relative risk of the primary outcome peaked within the first year of HCM diagnosis, highlighting that the first year after diagnosis is a vulnerable time window for mental disorders. Subgroup analyses showed consistent results irrespective of age, sex, and hypertension.

Comparison with other studies

Our results corroborate the findings from previous studies suggesting a possible association between HCM and mental disorders.[21,33] One study demonstrated that among 121 patients with HCM, 52.9 and 47.1% were depressed, according to the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale, respectively.[33] In a recent study investigating 820 patients with HCM, 23.4% had depression; screening was performed using the Hamilton Depression Rating Scale, and diagnosis was subsequently confirmed using the Structured Clinical Interview following the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria.[21]

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Table 3 Time-varying risk of mental disorders after diagnosis of hypertrophic cardiomyopathy

	Number	Event	PY	IR	Unadjusted HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
A composite of mood, anxiety, stress-related, and somatoform disorders								
<1 month								
Control	12 138	52	995	52.2	1 (reference)	<0.001	1 (ref.)	<0.001
HCM	4046	54	329	164.0	3.136 (2.143–4.589)		3.074 (2.096–4.508)	
1–12 months								
Control	12 082	389	11 862	32.8	1 (reference)	<0.001	1 (reference)	<0.001
HCM	3982	273	3824	71.4	2.178 (1.866–2.543)		2.281 (1.952–2.665)	
1–3 years								
Control	11 627	611	33 208	18.4	1 (reference)	<0.001	1 (reference)	<0.001
HCM	3653	359	10 234	35.1	1.928 (1.692–2.196)		2.087 (1.831–2.380)	
>3 years								
Control	9238	745	51 584	14.4	1 (reference)	0.030	1 (reference)	0.002
HCM	2713	251	15 013	16.7	1.171 (1.015–1.351)		1.258 (1.090–1.452)	
Mood disorders								
<1 month								
Control	12 138	9	997	9.0	1 (reference)	<0.001	1 (reference)	<0.001
HCM	4046	17	331	51.3	5.682 (2.533–12.747)		5.499 (2.432–12.430)	
1–12 months								
Control	12 082	104	12 008	8.7	1 (reference)	<0.001	1 (reference)	<0.001
HCM	3982	91	3912	23.2	2.688 (2.029–3.561)		2.825 (2.128–3.749)	
1–3 years								
Control	11 627	262	33 520	7.8	1 (reference)	<0.001	1 (reference)	<0.001
HCM	3653	154	10 471	14.7	1.888 (1.547–2.303)		2.021 (1.654–2.469)	
>3 years								
Control	9238	382	52 426	7.3	1 (reference)	0.065	1 (reference)	0.010
HCM	2713	134	15 357	8.7	1.204 (0.989–1.466)		1.300 (1.066–1.584)	
Anxiety/stress-related/somatoform disorders								
<1 month								
Control	12 138	44	996	44	1 (reference)	<0.001	1 (reference)	<0.001
HCM	4046	39	330	118	2.671 (1.736–4.110)		2.617 (1.696–4.038)	
1–12 months								
Control	12 082	318	11 898	27	1 (reference)	<0.001	1 (reference)	<0.001
HCM	3982	212	3855	55	2.059 (1.730–2.450)		2.148 (1.804–2.557)	
1–3 years								
Control	11 627	423	33 364	13	1 (reference)	<0.001	1 (reference)	<0.001
HCM	3653	274	10 319	27	2.113 (1.815–2.460)		2.284 (1.960–2.661)	
>3 years								
Control	9238	461	52 027	9	1 (reference)	0.089	1 (reference)	0.015
HCM	2713	156	15 167	10	1.171 (0.976–1.404)		1.255 (1.045–1.506)	

CI, confidence interval; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; IR, incidence rate per 1000 person-years; PY, person-years.
[a]Adjustment was performed for the covariates listed in Table 1 using Cox regression models, because the matching was broken when analyses by time of follow up, were conducted. Time since index date was used as underlying time scale.

However, these studies were small-sample, single-centre studies, making it difficult to generalize findings and draw firm conclusions. Furthermore, both studies evaluated depression incidence in a cross-sectional manner[21,33] and, thus, did not provide incidence rates.[34] Data on the incidence of mood disorders in general are lacking; however, a previous study reported that the incidence rate of depression was 13.9/1000 person-years,[35] similar to that of our study (13.4/1000 person-years for major depressive disorder). Hence, although study outcomes were defined using ICD-10-CM codes in our study, we believe that these outcomes are likely to be accurate, even if incomplete.

Our study showed that patients with HCM had a 74% higher risk of incident mood disorders, including depression, than those without HCM. Data regarding the incidence of anxiety/stress-related/somatoform disorders in patients with HCM are scarce. We demonstrated that the future risk of anxiety/stress-related/somatoform disorders was 81% higher in patients with HCM than in controls. However, since our study is a retrospective analysis of the claim database, the results should be interpreted cautiously given the biases inherent to this study design, such as the use of data collected for another purpose than that of the study of interest and possible confounding due to unmeasured

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factors. Given that the major strength of a prospective cohort study design is the accuracy of data collection regarding exposures, confounders, and outcomes, further studies examining the incidence of mental disorders in patients with HCM in a prospective and standardized manner are needed to validate our findings.

Another important novel finding in our study is the varying trend in the risk of mental disorders after HCM diagnosis. The relative risk of developing mental disorders was the highest within the first year after HCM diagnosis, suggesting the presence of a high-risk time window to which physicians should pay close attention. Considering that patients with HCM are generally informed that they could be at an increased but imprecise risk for cardiovascular events during HCM diagnosis, it is not surprising that the risk of mental health disorders peaked within the first year after diagnosis. Although the differences were attenuated thereafter, the risks of mental disorders associated with HCM remained significantly elevated beyond 3 years after diagnosis. A 1-year lag sensitivity analysis showed that the relative risk elevations were attenuated but remained significant. However, given the retrospective design of our study, the assessment of mental disorders during follow up was not systematically performed but was part of routine clinical practice. In this regard, the observation that the elevated risk of mental disorders decays over time might reflect changes in the frequency and comprehensiveness of assessment of mental disorders in patients with HCM who were apparently stable at long-term follow up. Further studies with standardized follow-up evaluation of mental disorders are required to confirm our findings. Collectively, our results consolidate previously reported associations between HCM and mental disorders and provide new information on the time course of the risk of subsequent mental disorders in patients with HCM.

Study perspectives

Multiple observations suggest that experiencing clinically confirmed mental disorders and emotional or physical stress may trigger cardiovascular events, such as arrhythmia, myocardial infarction, and SCD, in apparently healthy individuals.[7] These studies emphasize the need for a comprehensive and multidisciplinary approach integrating mental services into primary care, which has traditionally covered dimensions of physical wellness. Considering that patients with established CVDs, such as HF and AF, have increased susceptibility to mental disorders,[36,37] more attention should be paid to the risk of these potentially prevalent but neglected problems in HCM, with which HF and AF are also commonly comorbid. In this regard, it would be instructive and insightful to know whether the risk of mental disorders associated with HCM was modified by the presence of comorbidities. Our subgroup analysis showed that the risk of the primary outcome was consistently higher in patients with HCM than in matched controls in all strata. Notably, the increase in relative risk was more prominent in the subgroup aged ≤60 years and in those without hypertension than in their counterparts. Therefore, the elevated risk of mental disorders associated with HCM may not be solely driven by other cardiovascular comorbidities known to contribute to the risk of mental disorders.

Our study showed that patients with HCM had a persistently higher risk of mental disorders than controls over 3 years after HCM diagnosis, although the magnitude of the risk attenuated over time. This result suggests that there is an elevated and enduring risk of mental disorders in patients with HCM and consequently underlines the importance of sustaining efforts to detect these easy-to-miss problems during follow up. Further, comorbid mental disorders, such as depression and anxiety, are emerging modifiable risk factors for poor cardiovascular outcomes because these conditions serve as barriers to treatment adherence and lifestyle changes, including regular exercise, smoking cessation, and alcohol abstinence. Efforts to improve mental health can result in better outcomes of patients with CVDs, including HCM.[38] In view of this, our study highlights the need for long-term specialized care to address the mental health of patients with HCM to further improve their prognosis.

The risk of mental disorders can be influenced by medications frequently used in the treatment of HCM. Several studies suggest the potential associations between the medication and the risk of mental disorders, although results are conflicting. Specifically, a recent study assessed the associations of the 41 most used individual antihypertensive agents, including angiotensin agents, calcium antagonist, beta-blockers, and diuretics, with the risk of incident depression and found that the use of 9 individual hypertensive drugs might have a protective effect on the future risk of depression, while no drug was associated with an increased risk.[39] However, our study could not address whether and how medications influence the risk of mental disorders in patients with HCM, since data on the prescription of medications were only available at baseline, but not thereafter. Hence, we should acknowledge that our results are not free from the issue of time-varying confounding factors, such as changes in comorbidities and medications which may contribute to the development of mental disorders. Future studies can provide valuable insights into the potential psychological benefits or harms of the use of medications for the management of patients with HCM by examining the impact of medications on the risk of mental disorders in patients with HCM using a prospective study design.

Strengths and limitations

The merits of the present study include the population-based, propensity score-matched cohort study design, which provides extended control for confounders. Given that the main body of the preceding evidence was primarily derived from studies with small sample size, our study also had a large sample size that allowed us to perform meaningful subgroup analyses. This study also examined the time-varying effect of HCM on the risk of incident mental disorder, which was not performed in other previous studies. Characterizing the time-dependent risk pattern for mental disorders after HCM diagnosis may aid in the selection of actionable time windows for the implementation of appropriate screening and intervention strategies. Our study had some limitations. First, our observational study design had inherent limitations, including selection bias and the inability to ascertain causality. Approximately 70% of the initial sample was excluded in our study, although this was only for the purpose of assuring that our study population is free of the mental disorders of interest at baseline and obtaining a sample with complete data across all variables. We provided Supplementary material online, *Table S3* comparing the baseline characteristics between included and excluded individuals to give insight into possible selection bias due to non-random exclusion in our study. To mitigate concerns of reverse causality, individuals with previously diagnosed mental disorders were excluded. Second, residual confounding, particularly due to unmeasured covariates, is possible, although we used propensity score matching which is a suitable methodology to reduce the likelihood of confounding when analysing nonrandomized, observational data. The difference in follow-up duration could affect the difference in the number of events, but this factor was not included in propensity model in our study. Indeed, follow-up time was different in patients with HCM (4.1 years) and controls (4.6 years) ($P < 0.001$). However, considering that follow-up duration was shorter in patients with HCM than matched controls, the difference in follow-up time could attenuate our results and thus would not substantially change the conclusions of the study. Third, there have been concerns raised regarding the use of composite outcomes, such as the difficulty in interpreting the results, particularly in the setting of combining the components with large variability in importance to patients. However, all the individual components involved in the composite outcome used in our study (i.e. mood, anxiety, stress-related, and somatoform disorders) are of similar importance to individuals. Fourth, since the study population was derived from a single country, the results of

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our study may not be generalizable to other ethnicities. Our results cannot be also generalizable to the lowest income population, which is not covered by the Korean NHIS. Furthermore, since propensity matching was possible only in 80% of the eligible sample, we could not estimate the effect of HCM on the risk of mental disorders in these unmatched individuals, which hampers the generalizability of our findings. Fifth, the risk of mental disorders may differ according to whether HCM was diagnosed when patients had clinical events attributable to HCM, such as dyspnoea, palpitation, or syncope, vs. when they underwent routine screening or were referred for cascade testing due to diagnosis in a family member. However, we could not precisely test this hypothesis, since detailed patient-level clinical data are not available in the Korean NHIS database. We alternatively sought to assess the risk of mental disorders according to the receipt of implantable cardioverter defibrillators, which can partly reflect the presence of clinical events attributable to HCM, but the number of patients with HCM receiving this device was too small to provide a definite conclusion (28 cases). Further studies are needed to better understand which patients with HCM are at particularly high risk of developing mental disorders. This in-depth understanding would be especially important from a practical perspective, given that a patient–physician interaction is unique to HCM with a wide clinical spectrum that can manifest with HCM and the large amount of information that could be presented at the time a diagnosis of HCM is made. Sixth, our study is based on outcomes obtained from claim data, which are primarily used for billing purposes and may not precisely reflect individuals' medical status or health history. Furthermore, there are no available data on electrocardiogram, echocardiogram, and cardiac magnetic resonance in the Korean NHIS, which can assist in the differential diagnosis between HCM associated with hypertension and hypertensive heart disease. However, HCM is not likely to be misdiagnosed because individuals should satisfy strict diagnostic criteria for HCM to be registered in the RID system. Furthermore, the accuracy of NHIS claims data for the diagnosis of HCM and mental health disorders has been previously verified.[27,40] Finally, although family history of HCM and/or SCD may be potentially important confounders, these data were not available in the Korean NHIS database.

Conclusions

Diagnosis of HCM conferred higher risks of mental disorders, including mood, anxiety, stress-related, and somatoform disorders, particularly within 1 year after HCM diagnosis. These findings highlight the importance of screening for mental illnesses in patients with HCM and provide practical information on the high-risk time window during which clinicians should be cautious. Future studies are warranted to support our results and further investigate the risk of mental disorders in HCM and its association with long-term outcomes. Further, clinicians should consider mental health in addition to well-known physical consequences posed by HCM during follow up.

Authors' contributions

J.B.P., J.Y.Y., and H.K.K. contributed to the conception or design of the work. B.K. and K.H. contributed to the acquisition and analysis of data for the work. J.B.P., J.Y.Y., T.M.R., H.J.L., H.L., I.C.H., Y.E.Y., H.E.P., S.P.L., S.Y.C., Y.J.K., G.Y.C., K.H., and H.K.K. contributed to the interpretation of data for the work. J.B.P., J.Y.Y., and H.K.K. drafted the manuscript. B.K., T.M.R., H.J.L., H.L., I.C.H., Y.E.Y., H.E.P., S.P.L., S.Y.C., Y.J.K., G.Y.C., and K.H. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

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

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Conflict of interest: None declared.

Data availability

The data underlying this article were provided by Korean government after completing the request and approval process. The data will be available to the researchers on request to the Korean National Health Insurance Sharing Service (NHISS; https://nhiss.nhis.or.kr/), with approval by the Institutional Review Board. More details can be found at the homepage of the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do).

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