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Title: Comorbidity as a Mediator of Depression in Adults with Congenital Heart
Disease: A Population-Based Cohort Study

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Abstract

Background: The population of adults with congenital heart disease (CHD) has increased dramatically with a high prevalence of acquired cardiac and non-cardiac comorbidities. However, the relationship among CHD, physical comorbidities, and psychological health in this population is not well studied.

Aims: To investigate (1) the association between adult CHD and the occurrence of depression and (2) whether physical comorbidities mediated the association between CHD and the occurrence of depression.

Methods: This retrospective cohort study was followed from January 1, 2010 to December 31, 2013, based on the data from the National Health Insurance Research Database 2010 in Taiwan. We used mediation analysis in survival data to assess the mediated effect. The hazard ratios were adjusted by age, sex, area of residence, and estimated propensity scores.

Results: We recruited 2,122 adult CHD patients and 8,488 matched controls. Nearly half of patients diagnosed with simple CHD, 39.0% had complex CHD, and 11.2% had unclassified CHD. Adult CHD patients had a significantly higher risk of depression than matched controls (aHR=1.43 and 1.48, for all and complex CHD respectively, $p<0.05$). Coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) were the significant comorbidities mediating the relationship between adult CHD and depression, the proportions mediated by CAD or COPD were 35.5% and 12.9%, respectively.

Conclusions: Helping patients to prevent psychological and physical acquired disease is imperative. CAD is a potent mediator between CHD and depression, especially for patients with complex CHD.

Keywords: congenital heart disease, comorbidity, mediator, depression,
population-based cohort study, coronary artery disease

Comorbidity as a Mediator of Depression in Adults with Congenital Heart Disease: A Population-Based Cohort Study

Introduction

With advances in cardiovascular surgery and medical care technology, 90% of patient with congenital heart disease (CHD) survive into adulthood[1]. Most patients require long-term follow-up due to medical residua and sequelae [2, 3]. Furthermore, patients may have increased risk of having acquired cardiac and extra-cardiac complications [3, 4] and suffer from psychosocial challenges across their lifespan [2]. Understanding the common comorbidities and their association with CHD are essential for offering optimal care for adult CHD patients.

It is well known that postoperative cardiac residua and sequelae including valvular, ventricular, vascular, and electrophysiological abnormalities are common complications in the adult CHD population, and it may jeopardize patient's quality of life and long-term survival [5, 6]. Recently, a few studies have focused on the prevalence and impact of acquired comorbidities among adults with CHD. In adults with CHD, the prevalence of thyroid dysfunction was reported to range from 9% to 21%, neurologic disorder was 7% to 18%, chronic lung disease was around 5% [7, 8], gastro-intestinal tract and hepatology disorder was 12%, diabetes mellitus was 3%, renal disease was 7% [6], and cancer was 0.6% to 5% [6, 9]. While comparing with gender- and age-matched healthy adults, those with CHD had been reported with higher risks of acquired cardiac and extra-cardiac comorbidities. These comorbidities may impact both the work ability and life of the patients [7].

Growing up with CHD, patients also encounter psychosocial challenges, increasing their risk of psychological dysfunction. The prevalence of psychological morbidity in the adult CHD population is reported approximately 33% [10]. These

numbers are considered underestimated, since previous studies have found that, among adult CHD patients who are seemingly well-adjusted, 30-50% met the diagnostic criteria for mood, depressive, anxiety, or posttraumatic stress disorder [11, 12]. However, previous studies show no consensus conclusion when comparing the overall mental health status of CHD adults and healthy adults. While some studies have indicated adults with CHD had higher psychological risks [13-15], others have shown the psychological health of CHD adults was similar to healthy adults [16, 17] or even better than healthy controls [18, 19]. The inconsistent findings may be related to variations between age populations, geological areas, or measurement instruments. Among psychological diseases, depression is one of the leading causes of disability and death, even in the general population [20]. It is imperative to investigate the relationship between CHD and the occurrence of depression. Furthermore, the association between physical and psychosocial comorbidities in adults with CHD is not well studied yet. Therefore, this study aimed to investigate (1) the association between adult CHD and the occurrence of depression and (2) whether comorbidities mediated the association between adult CHD and the occurrence of depression.

Methods

This retrospective cohort study was conducted from January 1, 2010 to December 31, 2013. All subjects were followed until death or until the end of the study.

Data sources and ethic approval

This study was based on population-based data from the Longitudinal Health Insurance Database 2010 (LHID 2010) by the National Health Research Institute in

Taiwan (NHRI permission to release with No. NHIRD -104 - 413). The National Health Insurance (NHI) has been executed since 1995 and 99% of the 23 million Taiwanese are involved. The LHID 2010 database included one million random and representative individuals enrolled in the NHI program in 2010. There were no statistically significant differences in age, sex, or healthcare costs between the one million sample group and all the enrollees. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (No. 201510014W). The investigation conforms with the principles outlined in the Declaration of Helsinki.

Study cohorts

Adult patients with CHD were recruited if (a) >18 years old before January 01, 2010; (b) at least two outpatient service claims or one inpatient hospitalization claim diagnosed with CHD during 2002-2009. The definition of CHD ICD-9-CM codes in our study was consistent with Agarwal et al. [21] (Supplementary Table 1); (c) without any depression diagnosis for two years before recruitment to ensure the temporality of comorbidities and depression. To exclude any potential case of depression before recruitment, we used relatively liberal ICD-9CM codes (296.20-296.25, 296.30-296.35, 296.5, 296.6, 296.82, 296.90, 300.4, 309.0, 309.1, 311, 309.28) compared with the purpose of diagnostic certainty. These codes have been recommended for surveillance purposes [22].

The matched control cohort included adults who had neither CHD nor depression diagnosis before the recruitment. Furthermore, the control cohort was matched at a ratio of 4:1 to the CHD patients for age, sex, and area of residence by propensity score matching with the SAS macro ONETOMANY[23]. The estimated

propensity scores were included in the analysis to adjust the potential confounding effects of age, sex, and area of residence.

Variables

The primary outcome variable in this study was the occurrence of depression during the follow-up. Depression was defined as those who had one inpatient and/or one outpatient service claim (ICD-9CM codes: 296.20-296.25, 296.30-296.35, 300.4, 311) during 2010-2013. These codes are recommended when diagnostic certainty is necessary [22]. The positive predictive value (PPV) of the above diagnosis criteria of depression was 92.0% [22].

The common comorbidities for individuals were identified two years before the recruitment. In this study, we were interested in comorbidities that can be modified or prevented by changes in health-related behaviors, including diabetes (ICD-9CM codes: 250.x, 357.2, 362.01-362.07, 366.41), hypertension (ICD-9CM codes: 401.x-405.x), chronic obstructive pulmonary disease (COPD) (ICD-9CM codes: 490.x-494.x, 496.x), hyperlipidemia (ICD-9CM codes: 272.1-272.4), stroke (ICD-9CM codes: 433.x-434.x, 436.x), and coronary artery disease (CAD) (ICD-9CM codes: 410.x-414.x).

Control variables included age, sex, and area of residence for both adult CHD and matched cohort. All data were available from LHID 2010. We divided age into the following categories: 18-44, 45-64, and 65 years or older. We used the location of insurance application at the county/city level to determine the individual's area of residence. The definition of CHD complexity was categorized into three groups:

simple, complex, and unclassified, mainly following Agarwal et al. [21] except that patent ductus arteriosus (PDA) was recorded as simple complexity in this study.

Statistical analysis

Baseline demographic and clinical characteristics of the patients were presented as numbers and percentages for categorical variables. To examine the association between adult CHD and the occurrence of depression, cumulative incidences of depression were reported in adult CHD cohort and matched cohort, respectively. In addition, an adjusted hazard ratio (aHR) and the 95% confidence interval (CI) were used to examine the statistical significance using Cox proportional hazards model. Age, sex, area of residence, and estimated propensity scores were included in the Cox model to eliminate potential confounding effects.

We followed the mediation analysis approach proposed by Baron and Kenny [24] to assess whether each comorbidity acts as a mediator between adult CHD and the occurrence of depression. A comorbidity will be considered as a mediator if the following steps are satisfied. In Step 1, adult CHD (independent variable) significantly predicts the occurrence of depression (dependent variable). This demonstrates that the independent variable is associated with the outcome variable. In Step 2, adult CHD (independent variable) significantly predicts the comorbidity (mediator). In Step 3, the comorbidity (mediator) significantly predicts the occurrence of depression (dependent variable). In the final Step 4, comorbidity significantly predicts the occurrence of depression after adjusting the effect of adult CHD. A comorbidity functions as a full mediator when the association between CHD (independent variable) and depression (dependent variable) changed from significant

to non-significant, or as a partial mediator when the association between CHD and depression was still significant in the condition.

Traditionally, the above strategies were analyzed with general linear regression model; that is, the dependent variable and mediator were usually continuous. When the dependent variable was binary or survival data, estimating the direct and indirect effects using this traditional approach was not applicable. Therefore, we used the SAS macro provided by Valeri and VanderWeele [25] to estimate hazard ratios of the direct and indirect effects via comorbidity for adult CHD on the occurrence of depression.

In Valeri and VanderWeele's statistical approach, logistic regression analysis was conducted in Step 2 to examine whether adult CHD was associated with prevalent comorbidities. In addition, Cox proportional hazards model was used in the remaining Steps to examine the risk of depression. In each regression model, age, sex, area of residence, and estimated propensity scores were included in the regression model to adjust the potential confounding effects. Therefore, adjusted odds ratios (aORs) in logistic regression analysis, aHRs in Cox proportional hazards model, and their 95% confidence intervals were reported.

To assess the extent of mediated difference explained by comorbidity (mediator) for the effect of adult CHD on the occurrence of depression, we further calculated the proportion mediated in the aHRs of adult CHD in the model in Step 4 by the following formula [26]:

$$\frac{aHR_{Total\ Effect} - aHR_{Direct\ Effect}}{aHR_{Total\ Effect} - 1.0} \times 100\%$$

where the $aHR_{Total\ Effect}$ is the aHR of depression for people who have both adult CHD and the comorbidity compared with those who do not have adult CHD and the comorbidity, which is the product of aHRs of the direct and indirect effect. All data

analysis was implemented using SAS version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina), and a two-tailed *p*-value less than 0.05 was considered statistically significant.

Results

1. Study cohort characteristics

We recruited 2122 adult CHD patients and 8488 controls that were matched for sex, age, and area of residence in our study. The baseline characteristics of the two groups are summarized in Table 1. Of the 2122 adult CHD patients, female patients were the majority (62.0 %), the mean age was 40.6 years old (SD: 18.6) with most patients' age range between 18 to 44 years old (65.9 %), followed by 45-64 years old (19.9 %). Nearly half of the patients lived in Northern Taiwan (49.7 %). The most common CHD diagnosis was simple complexity (49.8 %), only eight patients with single ventricle heart disease (0.38 %).

2. The association between adult CHD and the occurrence of depression

The four-year cumulative incidence of depression was 39 cases per 1000 adult CHD patients and 28 cases per 1000 matched controls (Table 2). Adult CHD patients had a significantly higher risk of depression than the matched controls (aHR= 1.43; 95% CI= 1.11-1.83) after adjusted by sex, age, area of residence, and estimated propensity scores.

3. Mediation effect analyses

The following four steps examined the mediation effects of comorbidities. Step 1 of mediation analyses was to investigate the risk of adult CHD on the occurrence of

depression. This step was confirmed by our result, which showed that the risk of depression in adult CHD patients was 1.43 times of that of the matched controls (aHR= 1.43; 95% CI= 1.11-1.83) (Table 2), manifesting the association between adult CHD and depression.

For Step 2, the association between adult CHD and the comorbidities was shown in Table 3. Compared with the matched controls, adult CHD patients were more likely to have CAD (aOR, 6.48; 95% CI, 5.42-7.75), stroke (aOR, 2.32; 95% CI, 1.68-3.21), COPD (aOR, 2.08; 95% CI, 1.75-2.47), hypertension (aOR, 2.41; 95% CI, 2.07-2.81), hyperlipidemia (aOR, 1.73; 95% CI, 1.46-2.04), and diabetes (aOR, 1.60; 95% CI, 1.33-1.92). All comorbidities evaluated in this study were significantly associated with adult CHD, and therefore these comorbidities were further analyzed in the next step.

The results of Step 3 were reported in Table 4. The effects of the comorbidities on depression were found to be significant for CAD (aHR, 2.39; 95% CI, 1.70-3.35) and COPD (aHR, 2.07; 95% CI, 1.48- 2.89). According to the mediation analysis described by Baron and Kenny [24], COPD and CAD were candidates for mediators, and thus included in the analysis of Step 4.

In final Step 4, after including CHD and the comorbidities that were significant in Step 3 into the model, we found that the aHR of the indirect effect from adult CHD to depression via CAD was 1.11 (95% CI, 1.04-1.18) (Figure 1). The direct effect of adult CHD on depression was no longer significant after adjusting for CAD (aHR, 1.24; 95% CI, 0.96-1.61), demonstrating that CAD was a full mediator between adult CHD and depression. On the other hand, the indirect effect of HR from adult CHD to depression via COPD was 1.04 (95% CI, 1.01-1.07) (Figure 2). Nevertheless, the direct effect of adult CHD on depression was still significant after adjusting for

COPD (aHR, 1.36; 95% CI, 1.05-1.75), indicating that COPD was a partial mediator between adult CHD and the occurrence of depression. For the effect of CHD on depression, the proportions mediated by CAD or COPD were 35.5% and 12.9%, respectively, showing that CAD was a potent mediator.

4. Stratified analysis with CHD complexity

In the stratified analysis, we followed the same procedure to examine the mediation in each CHD complexity. In Step 1, the risk of depression analyses showed that patients with either complex CHD (aHR, 1.48, 95% CI, 1.01-2.18) or unclassified CHD (aHR, 2.22, 95% CI, 1.10-4.48) had significantly higher risk of depression compared with their matched controls (Supplementary Table 2). However, although the risk of depression was 22% higher in the patients with simple CHD than in the matched controls, this result was not significant (aHR, 1.22, 95% CI, 0.84-1.78).

For Step 2 (Supplementary Table 3), as the previous result, patients with either simple CHD or complex CHD were more likely to have CAD, stroke, COPD, hypertension, hyperlipidemia, and diabetes. Nevertheless, the risks of COPD and hyperlipidemia were not significantly different in unclassified CHD compared with matched controls. In Step 3 (Supplementary Table 4), CAD and COPD were candidates for mediators in complex CHD, and diabetes was the only candidate for the mediator in unclassified CHD.

In final Step 4, CAD and COPD were full mediators between complex CHD and depression (Supplementary Figure 1 & 2), but diabetes did not contribute mediating effect in unclassified CHD (Supplementary Figure 3). The indirect effect of aHR from complex CHD to depression through CAD and COPD was 1.42 (95% CI, 1.18-1.70)

and 1.06 (95% CI, 1.01-1.12), respectively. Moreover, CAD and COPD accounted for 81.9% and 19.0% of the total effect, respectively.

Discussion

To the best of our knowledge, this was the first study to investigate the comorbidities as mediators between adult CHD and depression using longitudinal data from the nationwide health database. There are two main results in this study. First, adult patients with CHD were more likely to have depression and selected non-communicable comorbidities than adults without CHD. Second, although adults with CHD had a higher risk for depression, we found that CAD and COPD were influential comorbidities mediating the relationship between adult CHD and depression, especially in patients with complex CHD.

Similar to our findings, previous studies in Western countries have also reported that adults with CHD are more likely to have cardiac and extra-cardiac diseases than the general population [6]. The etiology of non-communicable comorbidities in adults with CHD is multifactorial. Part of the causes is physical changes related to CHD, including both medical and surgical treatments [3]. On the other side, traditional risk factors such as health behavior, still play a role related to non-communicable comorbidities [27]. Previous studies have reported that health behavior in young adults with CHD is not optimal. One-third of young adults reported no sports engagement [28], 61% to 75% of patients reported some level of alcohol intake, 9.4% to 25% reported to have smoked tobacco [27, 28]. Therefore, the risk factors of acquired, non-communicable comorbidities and the practices of health behavior should be routinely assessed and addressed in CHD patients.

Depression is known to have a strong link with non-communicable diseases: depression increases the risk of non-communicable diseases and people with

non-communicable diseases have a higher risk of depression[20]. Our study not only demonstrated that CHD, which is a congenital disease, is associated with depression, but it also increases the risk of depression, especially in patients with complex and unspecified CHD. Previous studies show no consensus conclusion when comparing depression of CHD adults and healthy adults. The difference may be due to the cross-sectional study design, study population, or the use of different reporting instruments. The present study collected longitudinal data from a population-based database, and the definition of depression was based on clinical diagnosis instead of patient-reported outcomes, making our results comparably more reliable[19]. However, mental disorders have been found to be rarely diagnosed and commonly under-treated in adult CHD [11], implying that the cases of depression in adult CHD may still be underestimated in our study. Therefore, we suggest that both self-reporting scales and clinical diagnosis criteria should be used to identify patients with depression in the clinical circumstances[19].

To study the mechanisms underlying diseases is essential for disease prevention. The association between depression and CAD is considered bidirectional and multifaceted[20]. A recent meta-analysis reported the prevalence of depression is high in patients with CAD. Moreover, after adjustment for other confounding factors, depression was still a predictor for increased risk of cardiovascular events for CAD patients[29]. Previous studies have identified that the relationship between CAD and depression may be explained by biological factors including autonomic dysregulation, hypothalamus-pituitary-adrenal (HPA) axis dysfunction, and immune activation; as well as psychosocial factors such as social isolation and anxiety; and behavioral factors such as poor diet and inactivity[30]. On the contrary, the mechanisms linking CHD and depression have not been well examined. In our mediation analysis, we

revealed CAD and COPD are mediators between CHD and depression. Particularly, CAD fully mediated the relationship between CHD and depression. Therefore, the importance of chronic disease prevention, especially CAD and COPD, should be highly emphasized in adult CHD patients. Furthermore, due to the mutual and complex interaction, we suggest clinical practitioners to manage CAD and depressive symptoms if both are present.

Previous studies have reported that patients with single ventricle heart disease had unique physiology concerns and had the highest risk for ongoing morbidity and mortality[31], worth to be separated as a unique group for analysis. In this study, we only identified the common ventricle (ICD-9 CM: 745.3) as the single ventricle heart disease. Therefore, only eight patients were classified as single ventricle disease, and we think the patient number might be under-estimated. Patients with the diagnosis of hypoplastic left heart syndrome, double outlet right ventricle, pulmonary atresia with intact ventricular septum, atrioventricular canal, or Ebstein's anomaly may have single ventricle physiology. However, it may not be reliable to classify the patients with these ICD codes as single ventricle heart disease because part of them may have two functional ventricles. In addition, some patients with single ventricle heart disease may have very complex CHD without suitable coding of diagnosis, and hence the doctor may use other ICD-9 codes such as 746.9 or 746.89 (other congenital anomalies of heart). We recommend future research to examine the association between the single ventricle heart disease and the occurrence of depression and their mediators if detailed clinical data is available to distinguish patients with single ventricular from biventricular heart disease.

There are some limitations that should be considered in the present study. First, although we adjusted the confounding effects of age, sex, and area of residence by

propensity score matching to increase the comparability of the adult CHD group and the control group, potential residual confounders may influence the results. For instance, the results may be confounded by smoking status, drinking status, quality of life, physical activity [32], type of surgical repair, NYHA class, CHD complications, socioeconomic status, BMI, smoking history, and family history. However, these risk factors are not available in the NHIRD thus were not analyzed. Future studies can further explore the relationship among these potential risk factors, congenital heart disease, and depression. Second, the mean age of the CHD patients in our study was about 40 years old and only 17% of patients were older than 60 years old; thus, it may not be appropriate to extend the findings to the elderly population. Therefore, it is recommended to further evaluate the elderly with CHD in the future. Third, although we have used the ICD codes published in previous studies to define congenital heart disease and comorbidities, using different ICD codes may have different findings. When interpreting and adopting the results in this study, readers need to refer to the ICD we used. Fourth, we recruited individuals not having a diagnosis of depression in the previous two years before the recruitment. Someone without a diagnosis of depression in the previous years does not mean that there was not a history of depression, which would make someone more likely to have a later depression diagnosis. However, we had used the same criteria for both the CHD group and the matched control group to make the effect on both groups evenly and comparable. Fifth, previous studies have reported a significant portion of adults with CHD were lost to follow up[33], which may threaten the validity of a study no matter the data were collected on-site or from a database. The strength of this study database because the National Health Insurance (NHI) research database involved 99.9% of the 23 million Taiwanese. Furthermore, congenital heart diseases in Taiwan belong to

catastrophic illness, enabling patients with CHD having a discount. The CHD patients might lose to follow up in the cardiology clinic; however, they will be recorded once they visit a doctor and will be included in this study.

Conclusion

Adults with congenital heart disease have an increased risk of acquiring non-communicable comorbidities and depression. We found that comorbidities can be mediators between adult CHD and depression. Therefore, it would be of clinical importance that health care professionals offer screening tests for depression and provide preventive intervention of comorbidities, especially for CAD and COPD, to adult CHD patients at each ambulatory visit.

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Declaration of conflicting interests:

The authors declare that there is no conflict of interest.

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Table 1. Demographic Characteristics of CHD Cases and Matched Controls

Characteristic	<u>CHD (<i>n</i> = 2122)</u>		<u>Controls (<i>n</i> = 8488)</u>	
	<i>n</i> (%)		<i>n</i> (%)	
Sex				
Female	1315	(62.0)	5237	(61.7)
Male	807	(38.0)	3251	(38.3)
Age				
18-44	1399	(65.9)	5561	(65.5)
45-64	422	(19.9)	1675	(19.7)
≥ 65	301	(14.2)	1252	(14.8)
Area of residence				
Northern	1054	(49.7)	4327	(51.0)
Southern	534	(25.2)	2189	(25.8)
Western	495	(23.3)	1818	(21.4)
Eastern	39	(1.8)	154	(1.8)
CHD complexity				
Simple	1056	(49.8)	-	
Complex	828	(39.0)	-	
Unclassified	238	(11.2)	-	

Table 2. Adjusted Hazard Ratio (aHR) of Depression with CHD Cases and Matched Controls (STEP 1)

CHD	Depression <i>n</i> (%) ^a	aHR ^b	95% CI	p-value
Yes	82 (3.9)	1.43	1.11-1.83	0.006
No	234 (2.8)	1.00	Referent	

^a Cumulative incidence in the 4-year follow-up.

^b Age, sex, area of residence, and estimated propensity scores were included in the model to adjust the potential confounding effects.

Table 3. Adjusted Odds Ratios (aORs) of Predicting Comorbidities in CHD Cases and Matched Controls (STEP 2)

Comorbidity	CHD <i>n</i> (%) ^a	Controls <i>n</i> (%) ^a	aOR ^{b,c}	95% CIs	p-value
CAD	380 (17.9)	427 (5.0)	6.48	5.42-7.75	<0.001
Stroke	112 (5.3)	237 (2.8)	2.32	1.68-3.21	<0.001
COPD	231 (10.9)	501 (5.9)	2.08	1.75-2.47	<0.001
Hypertension	476 (22.4)	1231 (14.5)	2.41	2.07-2.81	<0.001
Hyperlipidemia	250 (11.8)	661 (7.8)	1.73	1.46-2.04	<0.001
Diabetes	205 (9.7)	584 (6.7)	1.60	1.33-1.92	<0.001

^a Cumulative incidence in the 4-year follow-up.

^b Age, sex, area of residence, and estimated propensity scores were included in the model to adjust the potential confounding effects.

^c Matched controls were set as reference group in the model.

Table 4. Adjusted Hazard Ratios (aHRs) of Developing Depression with Comorbidities (STEP 3)

Comorbidities	aHR ^a	95% CI	p-value
CAD	2.39	1.70-3.35	<0.001
Stroke	1.71	0.92-3.19	0.093
COPD	2.07	1.48-2.89	<0.001
Hypertension	1.31	0.94-1.83	0.107
Hyperlipidemia	1.32	0.93-1.88	0.123
Diabetes	1.44	0.99-2.09	0.057

^a Age, sex, area of residence, and estimated propensity scores were included in the model to adjust the potential confounding effects.

STEP 4:

Direct effect $aHR=1.24$ (95% CI, 0.96-1.61)

Indirect effect $aHR=1.11$ (95% CI, 1.04-1.18)

Proportion mediated = 35.5%

Figure 1 Mediated Effect of CAD between Depression and Adult CHD

STEP 4:

Direct effect $aHR=1.36$ (95% CI, 1.05-1.75)

Indirect effect $aHR=1.04$ (95% CI, 1.01-1.07)

Proportion mediated = 12.9%

Figure 2 Mediated Effect of COPD between Depression and Adult CHD

Supplementary

Supplementary Table 1. Complexity of CHD

Type of Lesion	ICD-9 code
Simple CHD	
Ventricular septal defect	745.4
Ostium secundum type atrial septal defect/ patent foramen ovale*	745.5
Other bulbus cordis anomaly or septal defect	745.8
Unspecified defect of septal closure	745.9
Congenital stenosis of aortic valve	746.3
Congenital insufficiency of aortic valve	746.4
Congenital mitral stenosis	746.5
Congenital mitral insufficiency	746.6
Coronary artery anomaly	746.85
Patent ductus arteriosus	747.0
Complex CHD	
Common truncus	745.0
Transposition of great vessels	745.1
Complete transposition of great vessels	745.10
Double outlet of right ventricle	745.11
Corrected transposition of great vessels	745.12
Other transposition of the great vessels	745.19
Tetralogy of Fallot	745.2
Common ventricle	745.3
Endocardial cushion defect	745.6
Endocardial cushion defect, unspecified type	745.60
Ostium primum defect	745.61
Other endocardial cushion defect	745.69
Cor biloculare	745.7
Anomalies of pulmonary valve	746.0
Pulmonary valve anomaly, unspecified	746.00
Pulmonary atresia	746.01
Pulmonary stenosis	746.02

Pulmonary valve anomaly, other	746.09
Tricuspid atresia and stenosis	746.1
Ebstein's anomaly	746.2
Hypoplastic left heart syndrome	746.7
Other unspecified anomalies of the heart	746.8
Subaortic stenosis	746.81
Cor triatriatum	746.82
Infundibular pulmonic stenosis	746.83
Obstructive anomalies of heart, NEC	746.84
Congenital heart block	746.86
Coarctation of aorta	747.1
Coarctation of aorta	747.10
Interruption of aortic arch	747.11
Anomalies of aorta	747.2
Anomaly of aorta, unspecified	747.20
Anomalies of aortic arch	747.21
Atresia and stenosis of aorta	747.22
Other congenital anomalies of the aorta	747.29
Anomalies of pulmonary artery	747.3
Anomaly of great veins	747.4
Anomaly of great veins, unspecified	747.40
Total anomalous pulmonary venous connection	747.41
Partial anomalous pulmonary venous connection	747.42
Other anomalies of great veins	747.49
Unclassified CHD	
Malposition of heart and cardiac apex	746.87
Other congenital anomalies of heart	746.89
Other congenital anomalies of heart	746.9

Supplementary Table 2. Adjusted Odds Ratios (aORs) of Comorbidities in adults CHD and Matched Controls Stratified by CHD Complexity (STEP 2)

	Depression <i>n</i> (%)	aHR^a	95% CI	p-value
All CHD vs matched controls				
Matched controls (<i>n</i> = 8488)	234 (2.8)	1.00	Referent	
All CHD (<i>n</i> = 2212)	82 (3.9)	1.43	1.11-1.83	0.006
Simple CHD vs matched controls				
Matched controls (<i>n</i> = 4224)	116 (2.8)	1.00	Referent	
Simple CHD (<i>n</i> = 1056)	35 (3.3)	1.22	0.84-1.78	0.304
Complex CHD vs matched controls				
Matched controls (<i>n</i> = 3312)	96 (2.9)	1.00	Referent	
Complex CHD (<i>n</i> = 828)	35 (4.2)	1.48	1.01-2.18	0.046
Unclassified CHD vs matched controls				
Matched controls (<i>n</i> = 952)	22 (2.3)	1.00	Referent	
Unclassified CHD (<i>n</i> = 238)	12 (5.0)	2.22	1.10-4.48	0.027

^a Age, sex, area of residence, and estimated propensity scores were included in the model to adjust the potential confounding effects.

Supplementary Table 3. Adjusted Odds Ratios (aORs) of Comorbidities in adult CHD and Matched Controls Stratified by CHD Complexity (STEP 2)

Comorbidity	CHD <i>n</i> (%)		Matched controls <i>n</i> (%)		aOR ^{a,b}	95% CIs	p-value
Simple CHD (<i>n</i> = 1056) vs matched controls (<i>n</i> = 4224)							
CAD	91	(8.6)	147	(3.5)	3.28	2.41-4.47	< 0.001
Stroke	24	(2.3)	37	(0.9)	2.81	1.63-4.87	< 0.001
COPD	84	(8.0)	191	(4.5)	1.88	1.43-2.48	< 0.001
Hypertension	158	(15.0)	427	(10.1)	2.00	1.57-2.56	< 0.001
Hyperlipidemia	84	(8.0)	263	(6.2)	1.37	1.04-1.80	< 0.023
Diabetes	82	(7.8)	212	(5.0)	1.78	1.33-2.34	< 0.001
Complex CHD (<i>n</i> = 828) vs matched controls (<i>n</i> = 3312)							
CAD	264	(31.9)	240	(7.3)	10.67	8.35-13.65	< 0.001
Stroke	30	(3.6)	72	(2.2)	1.80	1.15-2.98	0.010
COPD	128	(15.5)	260	(7.9)	2.34	1.84-2.85	< 0.001
Hypertension	276	(33.3)	690	(20.8)	2.76	2.23-3.42	< 0.001
Hyperlipidemia	149	(18.0)	335	(10.1)	2.16	1.72-2.70	< 0.001
Diabetes	101	(12.2)	346	(9.8)	1.35	1.05-1.75	0.021
Unclassified CHD (<i>n</i> = 238) vs matched controls (<i>n</i> = 952)							
CAD	25	(10.5)	40	(4.2)	3.95	2.12-7.39	< 0.001
Stroke	10	(4.2)	13	(1.7)	4.25	1.64-10.99	0.003
COPD	19	(8.0)	50	(5.3)	1.72	0.96-3.08	0.070
Hypertension	42	(17.7)	114	(12.0)	2.57	1.49-4.45	< 0.001
Hyperlipidemia	17	(7.1)	63	(6.6)	1.14	0.63-2.06	0.674
Diabetes	22	(9.2)	46	(4.8)	2.76	1.46-5.23	0.002

^a Age, sex, area of residence, and estimated propensity scores were included in the model to adjust the potential confounding effects.

^b Matched controls were set as reference group in the model.

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Supplementary Table 4. Adjusted Hazard Ratios (aHRs) of Developing Depression with Comorbidities Stratified by CHD complexity (STEP 3)

Comorbidities	aHR^a	95% CI	p-value
Complex CHD and their matched controls (<i>n</i> = 4140)			
CAD	2.75	1.78-4.25	< 0.001
Stroke	1.82	0.83-4.01	0.135
COPD	2.17	1.38-3.42	0.001
Hypertension	1.34	0.86-2.08	0.202
Hyperlipidemia	1.18	0.73-1.93	0.499
Diabetes	1.42	0.86-2.33	0.173
Unclassified CHD and their matched controls (<i>n</i> = 1190)			
CAD	1.03	0.28-3.78	0.962
Stroke	0.95	0.12-7.57	0.964
Hypertension	1.75	0.56-5.46	0.334
Diabetes	3.61	1.21-10.75	0.021

^a Age, sex, area of residence, and estimated propensity scores were included in the model to adjust the potential confounding effects.

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STEP 4:

Direct effect $aHR=1.04$ (95% CI, 0.69-1.59)

Indirect effect $aHR=1.42$ (95% CI, 1.18-1.70)

Proportion Mediated = 81.9%

Supplementary Figure 1. Mediator effect of CAD on Depression in complex CHD

STEP 4:

Direct effect $aHR=1.37$ (95% CI, 0.93-2.03)

Indirect effect $aHR=1.06$ (95% CI, 1.01-1.12)

Proportion Mediated = 19.0%

Supplementary Figure 2. Mediator effect of COPD on Depression in complex CHD

STEP 4:

Direct effect aHR=2.10 (95% CI, 1.03-2.46)

Indirect effect aHR=1.04 (95% CI, 0.97-1.12)

Proportion Mediated = 7.2%

Supplementary Figure 3. Mediator effect of Diabetes on Depression in unclassified CHD