


Menopausal symptoms and risk of heart failure: a retrospective analysis from Taiwan National Health Insurance Database

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Abstract

Aims Women with menopausal symptoms show evidence of accelerated epigenetic ageing, vascular aging and low-grade systemic inflammation status. However, data are limited regarding menopausal symptoms and risk of heart failure (HF). We aimed to explore the impact of menopausal symptoms on risk of HF.

Methods We included 14 340 symptomatic menopausal women without a history of coronary heart disease (CHD) or HF from the Taiwan National Health Insurance Research Database as the experimental cohort. We included 14 340 asymptomatic women matched for age and comorbidities as controls. We surveyed possible comorbidity-attributable risks of HF and assessed whether menopausal symptoms play a role in risk of HF. Additional analyses were conducted to ascertain the association of CHD and HF in different risk factor burdens categories in both cohorts and CHD was applied as a sensitivity analysis.

Results The incidence of HF was not significantly lower in the experimental than in the control cohort (4.87 vs. 5.06 per 1000 person-years, $P = 0.336$). Participants with a higher comorbidity burden had a proportionally increased risk of HF and CHD in both cohorts. The burden of risk factors had a greater impact on risk of HF in the control than in the experimental cohort (\geq five risk factors, adjusted hazard ratio 25.69 vs. 14.75). Participants undergoing hormone therapy had no significant effect on the risk of HF, regardless of the presence or absence of menopausal symptoms. Subgroup analysis revealed that compared with the control cohort, the risk of HF in the experimental cohort did not increase significantly in all subgroups.

Conclusions Menopausal symptoms were associated with CHD risk but not with risk of HF. Traditional risk factors rather than menopausal symptoms play important roles in the HF risk among middle-aged women.

Keywords Menopausal symptoms; Coronary heart disease; Heart failure

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Introduction

The menopause transition is a period of reproductive ageing that occurs directly before the onset of many chronic diseases.¹ Menopause symptoms (mainly hot flashes and vasomotor symptoms) have been linked to adverse health indicators, including cardiovascular disease (CVD) risk,^{2–4} diabetes,⁵ hypertension,⁶ lower bone density⁷ and increased

risk of new-onset depressive or anxiety disorders in later life.⁸ Furthermore, women with menopausal symptoms show evidence of accelerated epigenetic ageing in the Women's Health Initiative (WHI) study,⁹ and these women had associated vascular ageing¹⁰ and low-grade systemic inflammation status.¹¹ Thus, menopause can be conceptualized as a time of accelerated biologic ageing beyond chronologic ageing alone.¹²

Heart failure (HF) is a global problem affecting around 26 million people worldwide, and the HF prevalence increases substantially with ageing in both sexes, particularly among patients age >64 years. Furthermore, older women are at greater risk than men, with a notably higher incidence of heart failure with preserved ejection fraction (HFpEF) in postmenopausal women.¹³ Management of HFpEF is challenging because effective evidence-based treatments for HFpEF are lacking.¹⁴ Most treatments for HFpEF are aimed at risk factors and comorbidities.¹⁵ Established risk factors for HF, including hypertension, diabetes and obesity, are common in both sexes, but many of these risk factors convey a differential risk in women as compared with men.¹⁶ Menopausal symptoms may be a sex-specific risk factor unique to women. We postulated that women with severe menopausal symptoms might be regarded as having more profound biological ageing signals than those without menopausal symptoms. Our previous study indicated that menopausal symptoms are significantly associated with coronary heart disease (CHD).¹⁷ However, it remains unknown whether the presence of menopausal symptoms can predict clinical HF events or is explained by comorbidity-attributable risk burden. We used the same dataset as in our previous work and explored the possible comorbidity-attributable risk burden to investigate the impact of menopausal symptoms on the risk of HF, which is a different approach method compared with our previous work. Additional analyses were conducted to ascertain the association of CHD in different risk factor burdens categories and was applied as a sensitivity analysis. In addition, we aimed to explore which comorbidity-attributable risk is most crucial for Asian postmenopausal women with HF.

Methods

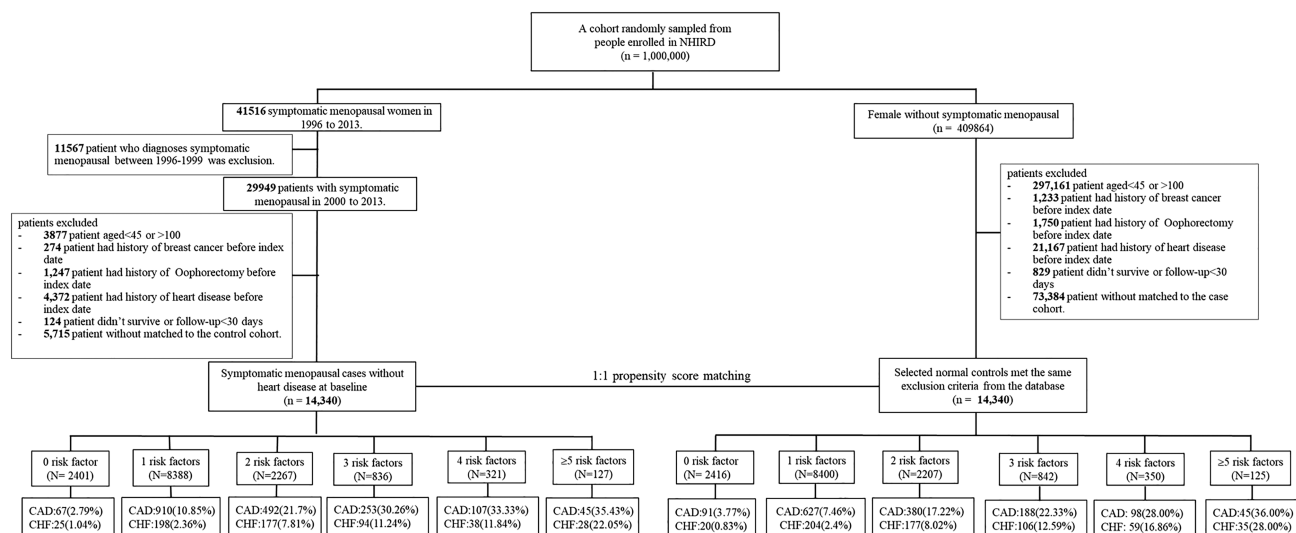
Data source

Our study data were retrieved from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD contains the claims data of all insurants of Taiwan's National Health Insurance (NHI) programme, which provides coverage to 99% of the population of Taiwan. The diagnostic codes for identifying diseases in the NHIRD are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). All personal identifiers were encrypted by the NHI Administration prior to study commencement. The database contains healthcare information including birth date, sex, prescription drugs, medical procedures and diagnostic codes. This investigation is a retrospective database-based study, with no clinical data available. This study was exempt from full review and was approved by the Institutional Review Board of Changhua Christian Hospital (approval number 170411). The requirement for informed consent was waived.

Study population

A cohort of approximately 1 000 000 patients over the period 1996–2013 was randomly sampled from the NHIRD. A total of 41 516 women with menopausal symptoms were selected (with diagnostic code ICD-9-CM 627.2—Symptomatic menopausal or female climacteric states). All the selected subjects met the following conditions: The diagnosis of symptomatic menopause (diagnostic code ICD-9-CM 627.2) was performed

Figure 1 Study flow chart.



by a gynaecologist. Subjects must receive at least three outpatient diagnosis of ICD-9-CM 627.2 within 1 year. We used a 4-year look-back period (1996–1999) to identify women with newly diagnosed symptomatic menopausal transition by excluding pre-existing diagnoses (*Figure 1*). We excluded 11 567 women with a symptomatic menopausal transition diagnosis during the look-back period. The index date (enrolment date) was defined as the first date when an eligible woman was diagnosed with symptomatic menopause using diagnostic code ICD-9-CM 627.2. This date was also assigned to the matched comparison participants as the date of entry into the study. We excluded patients with CHD, HF, breast cancer or oophorectomy before the index date; those aged <40 or >100 years; those with incomplete demographic data; and those who did not survive for >30 days after receiving a diagnosis of symptomatic menopause. The control cohort comprised patients without a history of CHD, HF, breast cancer, oophorectomy or menopausal symptoms before the index date. The control cohort was selected using 1:1 propensity score matching. A flow chart of the cohort selection process is presented in *Figure 1*. To balance the measured covariates between the two study cohorts, we calculated the propensity score using multivariate logistic regression to predict the likelihood of menopausal symptoms for each patient. For each patient with menopausal symptoms, one control without menopausal symptoms was selected with matching by age, calendar year of index date and propensity score. We used the nearest-neighbour algorithm with a caliper of 0.1 standard deviation (SD) units to generate matched pairs. Details of the propensity score model are described in our previous work.¹⁷

Outcome measures and potential risk factors

The primary outcome was the development of HF following the index date. We examined ICD-9-CM codes in the patients' records to determine outcomes and comorbidities. Both the symptomatic menopausal and control cohorts were followed up from the date of study enrolment to the date of the first occurrence of HF, date of withdrawal from the NHI programme or the end of 2013. The date of withdrawal from the NHI programme has been recognized as an accurate and reliable proxy for the date of death in Taiwan.¹⁸ HF were identified on the basis of the diagnostic code (ICD-9-CM 428.0) recorded for at least three outpatient clinic visits or at least one hospital admission. The mean follow-up period was 8.5 years (SD 4.7 years). Potential risk factors were defined based on the previous literature,¹⁹ and the possible comorbidity-attributable risks of cardiovascular disease were surveyed. Risk factors were defined as age ≥ 65 years, monthly income <TWD 25 000, obesity, hypertension, diabetes mellitus, hyperlipidaemia, stroke, chronic kidney disease, peripheral arterial occlusion disease, dysrhythmia and chronic

obstructive pulmonary disease. In this study, we used monthly income calculated from the NHI premium as a proxy for individual socio-economic status. Individuals were classified into three income groups: (1) low (<TWD 15 840 per month) and denoted as 0; (2) medium (TWD 15 840–TWD 25 000 per month) and denoted as 1; and (3) high (>TWD 25 000 per month) and denoted as 2. The classification was based on the minimum monthly wage for the year 2006 in Taiwan (TWD 15 840). According to data released in 2015 by the Ministry of Labor in Taiwan, the average salary after graduation was TWD 25 000. Furthermore, we analysed participants in both cohorts with variable risk factor burdens to test whether a higher risk factor burden proportionally increased the risk of HF.

Approximately estimate the menopausal symptoms and proxy measures of symptomatic menopause duration

From NHIRD, we cannot identify the menopausal symptoms directly. We tried to approximately estimate the menopausal symptoms by the symptomatic menopausal diagnosis with corresponding medications. The surrogate indicator of the duration of symptomatic menopause is based on the length of time between the first and last symptomatic menopause-related visits reported by the gynaecologist.

Statistical analysis

The demographic data and other clinically relevant data of both cohorts are presented as proportion and mean \pm SD. A standardized difference (StD) of more than 0.1 indicated significant heterogeneity between the two cohorts. A Cox proportional hazards model was used to estimate the relative risk of HF in the symptomatic menopausal cohort and the control cohort. Adjusted hazard ratios (aHRs) were estimated using multivariate Cox analysis, which was adjusted for confounders, namely, age, monthly income, comorbidities and long-term medication use. Because comorbidities may not only be present at baseline but may also develop during follow-up, comorbidities were modelled using non-reversible time-dependent binary covariates for event analyses. Deaths prior to the development of HF were considered competing risks. Therefore, we conducted competing risk survival analysis using the Fine–Grey subdistribution hazards model. The association of symptomatic menopausal transition with subsequent development of HF was reported as subhazard ratios (SHRs) and 95% confidence intervals (CIs). All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Two-tailed *P*-values of <0.05 were considered statistically significant.

Table 1 Baseline characteristics of women according to risk factors burden

	Number of risk factors ^a					P-value	P-trend
	0	1	2	3	4		
Sample size	4817	16 788	4474	1678	671	252	
Age	49.26 ± 3.14	50.86 ± 4.66	55.73 ± 8.56	58.94 ± 9.06	61.64 ± 9.53	66.21 ± 8.55	<0.001
Monthly income (NTD)							
0	0(0%)	8485(50.54%)	2450(54.76%)	986(58.76%)	433(64.53%)	173(68.65%)	<0.001
1	0(0%)	7617(45.37%)	1771(39.58%)	632(37.66%)	233(34.72%)	78(30.95%)	<0.001
2	4,817(100%)	686(4.09%)	253(5.65%)	60(3.58%)	5(0.75%)	1(0.4%)	<0.001
Comorbidities at baseline							
Hypertension	0(0%)	284(1.69%)	1617(36.14%)	1149(68.47%)	566(84.35%)	233(92.46%)	<0.001
Hyperlipidaemia	0(0%)	106(0.63%)	623(13.92%)	626(37.31%)	356(53.06%)	177(70.24%)	<0.001
Diabetes mellitus	0(0%)	62(0.37%)	432(9.66%)	495(29.5%)	366(54.55%)	197(78.17%)	<0.001
Obesity	0(0%)	17(0.1%)	36(0.8%)	30(1.79%)	20(2.98%)	8(3.17%)	<0.001
Chronic kidney disease	0(0%)	20(0.12%)	107(2.39%)	98(5.84%)	79(11.77%)	67(26.59%)	<0.001
Stroke	0(0%)	10(0.06%)	75(1.68%)	112(6.67%)	111(16.54%)	84(33.33%)	<0.001
COPD	0(0%)	143(0.85%)	744(16.63%)	269(16.03%)	148(22.06%)	87(34.52%)	<0.001
PAOD	0(0%)	4(0.02%)	43(0.96%)	19(1.13%)	10(1.49%)	11(4.37%)	<0.001
Dysrhythmia	0(0%)	32(0.19%)	141(3.15%)	66(3.93%)	48(7.15%)	22(8.73%)	<0.001
Menopausal symptoms	2401(49.84%)	8388(49.96%)	2267(50.67%)	836(49.82%)	321(47.84%)	127(50.4%)	0.828
Long-term use of medications ^b							
Cardiovascular medication	118(2.45%)	456(2.72%)	742(16.58%)	635(37.84%)	347(51.71%)	164(65.08%)	<0.001
Diabetic drugs	4(0.08%)	44(0.26%)	210(4.69%)	276(16.45%)	224(33.38%)	141(55.95%)	<0.001
Statin	7(0.15%)	64(0.38%)	130(2.91%)	186(11.08%)	138(20.57%)	89(35.32%)	<0.001
Hormonal replacement therapy	419(8.7%)	1848(11.01%)	594(13.28%)	258(15.38%)	93(13.86%)	37(14.68%)	<0.001
Oestrogens	164(3.4%)	862(5.13%)	317(7.09%)	156(9.3%)	60(8.94%)	28(11.11%)	<0.001
Progestogens	104(2.16%)	632(3.76%)	242(5.41%)	102(6.08%)	42(6.26%)	19(7.54%)	<0.001
Progestogens and oestrogens in combination	235(4.88%)	934(5.56%)	261(5.83%)	101(6.02%)	30(4.47%)	10(3.97%)	0.154
Outcome							
CHD	158(3.28%)	1537(9.16%)	872(19.49%)	441(26.28%)	205(30.55%)	90(35.71%)	<0.001
HF	45(0.93%)	402(2.39%)	354(7.91%)	200(11.92%)	97(14.46%)	63(25%)	<0.001

^aThe risk factor was defined as age ≥65 years, income < TWD25000, obesity, hypertension, diabetes mellitus, hyperlipidaemia, stroke, chronic kidney disease (CKD), peripheral arterial occlusion disease (PAOD), dysrhythmia and chronic obstructive pulmonary disease (COPD).

^bDefined as drug prescription for at least 3 consecutive months.

Results

Baseline characteristics of women according to risk factor burden

Table 1 lists the baseline demographic data of enrolled patients according to risk factor burden. The mean age of the control vs. the experimental cohort was 52.2 ± 6.71 vs. 52.22 ± 6.59 years old. The mean age of patients in each risk factor subgroup increased proportionally as the number of risk factors increased. The monthly income status was inversely correlated with risk factor burden. The top three major comorbidities were hypertension, hyperlipidaemia and Type 2 diabetes mellitus. The incidence of CHD and HF was proportionally increased with increased number of risk factors.

Incidence and risk of HF in symptomatic menopausal and control cohorts

During the follow-up period, the number of HF events in the control and symptomatic menopausal cohorts was 601 (4.83 per 1000 person-years) and 560 (4.47 per 1000 person-years), respectively (Table 2). Kaplan–Meier analysis revealed that the cumulative incidence of HF was not significantly different in the cohorts (log-rank test, $P = 0.336$) (Figure 2). Four models were used to adjust the risk of HF in the symptomatic menopausal cohort vs. the control cohort (Table 2). In Model 1, after propensity score matching, the risk of HF was insignificant (crude HR = 0.945, 95% CI = 0.842–1.06, $P = 0.3356$). In Model 2, after propensity score adjustment, the risk of HF was non-significantly different (aHR = 0.941, 95% CI = 0.838–1.056, $P = 0.2994$). In Model 3, after adjustment for all the confounders listed in Table 1, the risk of HF was non-significantly different (aHR = 0.965, 95% CI = 0.853–1.092, $P = 0.5689$). In Model 4, which was the fully adjusted model, the risk of HF remained non-significant after fully adjusting the model (aHR = 0.916, 95% CI = 0.801–1.048, $P = 0.2003$).

Relationship between risk factor burden and incidence of CHD or HF among symptomatic menopausal and control cohorts

The incidence of CHD in the symptomatic menopausal cohort was significantly higher than in the control cohort for each risk factor burden category (Figure 3A). However, the incidence of HF in the control cohort was higher than in the symptomatic menopausal cohort for each risk factor burden category (Figure 3B). Participants with a higher multimorbidity burden

Table 2 Incidence and risk of HF in symptomatic menopausal and control cohorts

HF	Event	PY	Incidence ^a	Model 1		Model 2		Model 3		Model 4	
				HR (95% CI)	P-value ^a	Adj.HR (95% CI)	P-value ^a	Adj.HR (95% CI)	P-value ^a	Adj.HR (95% CI)	P-value ^a
Control cohort	601	124552.32	4.83(4.44,5.21)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
SM cohort	560	125145.98	4.47(4.1,4.85)	0.945 (0.842,1.06)	0.3356	0.941 (0.838,1.056)	0.2994	0.965 (0.853,1.092)	0.5689	0.916 (0.801,1.048)	0.2003

Adj.HR, adjusted hazard ratio; CI, confidence interval; HF, heart failure; HR, hazard ratio; PY, person-years; SM, symptomatic menopausal.

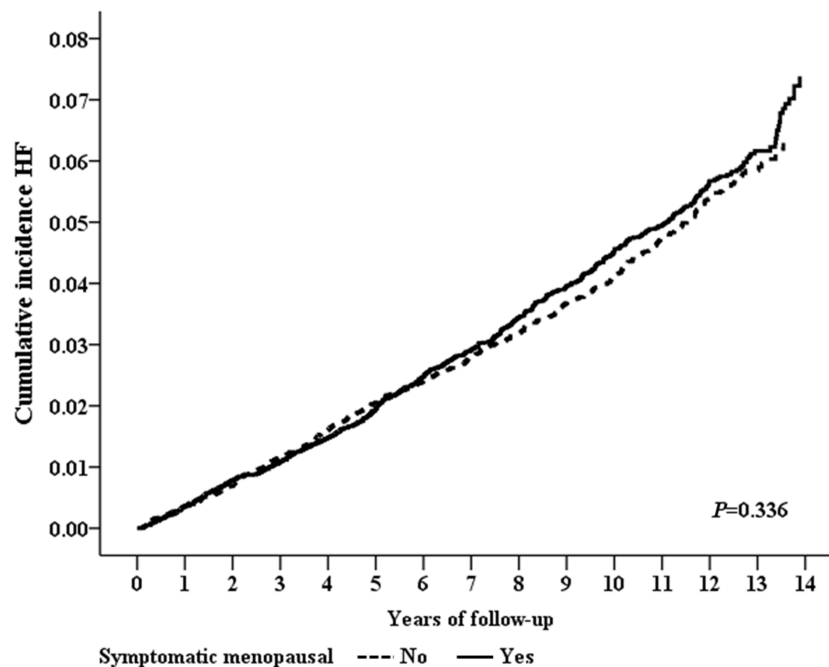
Model 1: Propensity score matched.

Model 2: Adjusted for propensity score.

Model 3: Adjusted for all variables listed in Table 1. Table 1 variables include age, monthly income, comorbidities and long-term use of medications.

Model 4: Adjusted for all variables listed in Table 1, and comorbidities and medication use were time-dependent covariates.

^aPer 1000 person-years. All analyses incorporated in regard to death as competing risks.

Figure 2 Cumulative incidence of HF in symptomatic menopausal and control cohorts.

(greater number of risk factors) had a proportionally increased risk of HF and CHD in both cohorts.

in the symptomatic menopausal and control cohorts, respectively.

Impact of risk factor burden on the HF risk in both cohorts

The accumulated number of risk factors showed greater impacts on the risk of HF in the control cohort than in the symptomatic menopausal cohort (\geq five risk factors, aHR 25.69 vs. 14.75). A magnitude of more than two risk factors had a greater impact on risk of HF in the control cohort than symptomatic menopausal cohort (Table 3).

Hormone therapy and risk of HF

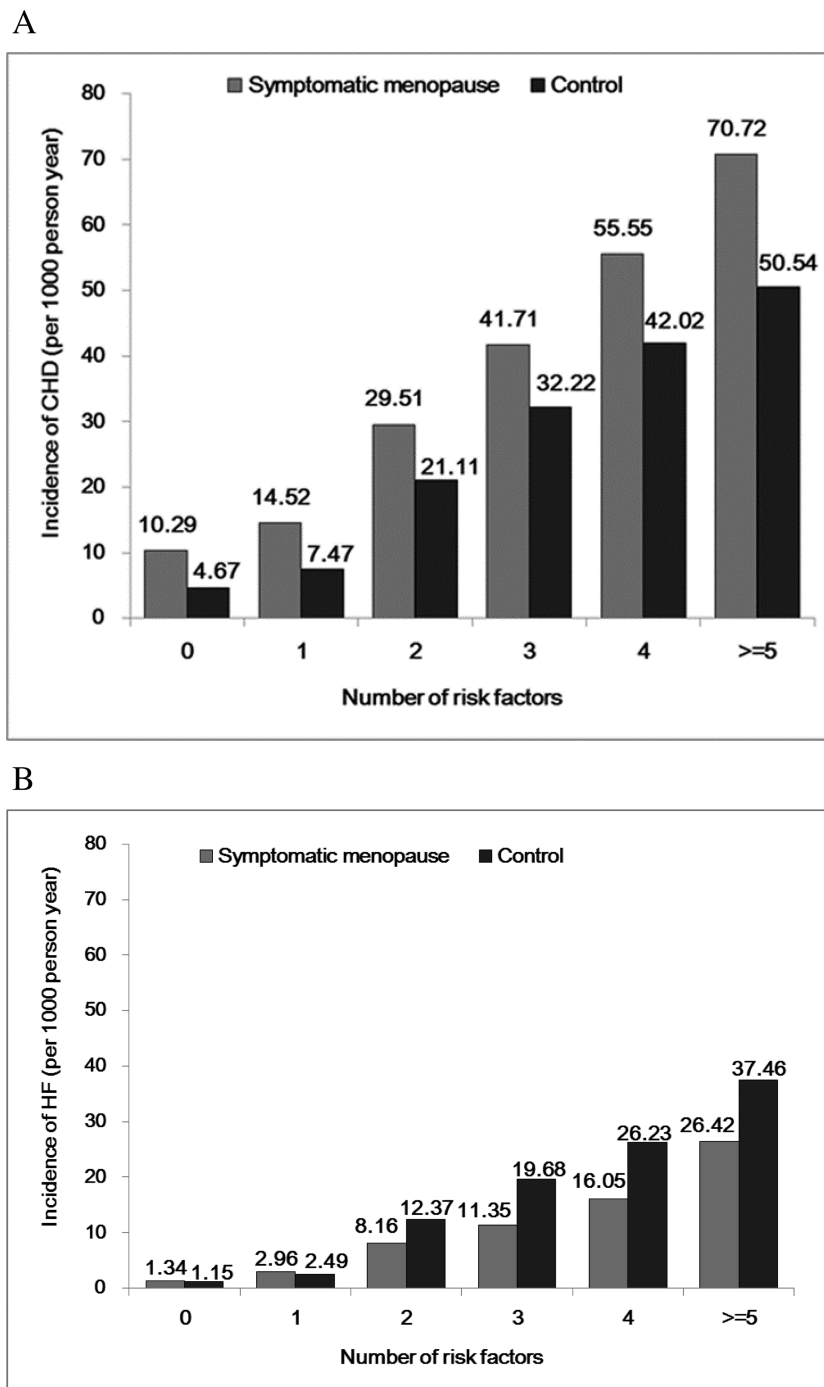
All patients who received hormone therapy did not increase risk of HF (crude HR = 1.057, 95% CI = 0.923–1.211, $P = 0.4203$). These results were non-significant after adjustment for the variables listed in Table 1, including age, sex, monthly income, comorbidity and long-term medications (aHR = 0.932, 95% CI = 0.796–1.092, $P = 0.3822$; Table 4). Stratifying by with or without hormone therapy, aHRs for HF in hormone users were 0.962 (95% CI = 0.809–1.145, $P = 0.6651$) and 0.836 (95% CI = 0.535–1.308, $P = 0.4335$)

Subgroup analyses of the risk of HF between symptomatic menopausal and control cohorts

Subgroup analyses were performed to determine the association between symptomatic menopause and the risk of HF for the age groups of <50 and ≥ 50 years, subgroups with or without using medication focusing on beta blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in both cohorts. The results revealed that the symptomatic menopausal cohort had not a significantly higher risk of HF in all subgroups (Table 5).

Approximately estimate the menopausal symptoms and duration of symptomatic menopausal transition

We tried to approximately estimate the menopausal symptoms by the symptomatic menopausal diagnosis with corresponding medications. It revealed that 88.7% subjects had received hormone therapy, 76.4% had received anxiolytics therapy, 28.1% had received beta-blocking agents, and 23.1% had received hypnotics (Table S1). This finding was

Figure 3 Relation between number of risk factors and incidence of CHD (A) or HF (B) among symptomatic menopausal cohort and control cohort.

in suggestive of the major menopausal symptoms such as vasomotor symptoms, hot flashes, anxiety and insomnia in our study group. Among symptomatic menopausal group receiving hormone therapy, only 11.33% subjects with

long-term hormone therapy (duration: 3.3 ± 3.4 years), which was reported in our previous work.¹⁷ The duration of symptomatic menopausal transition was 4.15 ± 3.46 years.

Table 3 The impact of risk factors on the risk of HF in both cohorts

Number of risk factor	Symptomatic menopausal cohort			
	cHR (95% CI)	P-value	aHR (95% CI) ^a	P-value
0	1 (reference)		1 (reference)	
1	2.18(1.57,3.04)	<.0001	2.18(1.57,3.04)	<.0001
2	5.99(4.28,8.37)	<.0001	5.70(4.07,7.98)	<.0001
3	8.29(5.84,11.78)	<.0001	7.49(5.22,10.74)	<.0001
4	11.55(7.87,16.93)	<.0001	10.19(6.81,15.23)	<.0001
≥5	18.77(12.32,28.60)	<.0001	16.42(10.50,25.70)	<.0001
P for trend	<.0001		<.0001	

All analyses incorporated in regard to death as competing risks.

^aModel was adjusted for medication use at baseline.

^bModel was adjusted for medication use as time-dependent covariates

^cP interaction was test whether presence of interaction effect between menopause symptoms and number of risk factor.

Table 3 (continued)

Number of risk factor	Symptomatic cohort		Control cohort		P _{interaction} ^c
	cHR (95% CI)	P-value	aHR (95% CI) ^a	P-value	
0	1 (reference)		1 (reference)		
1	2.11(1.62,2.74)	<.0001	2.11(1.62,2.75)	<.0001	0.8546
2	10.05(7.79,12.97)	<.0001	10.04(7.77,12.97)	<.0001	0.0271
3	15.78(12.20,20.41)	<.0001	15.87(12.21,20.63)	<.0001	0.0055
4	20.62(15.89,26.75)	<.0001	21.33(16.26,27.98)	<.0001	0.0127
≥5	28.10(21.59,36.57)	<.0001	30.50(23.01,40.42)	<.0001	0.0983
P for trend	<.0001		<.0001	<.0001	

All analyses incorporated in regard to death as competing risks.

^aModel was adjusted for medication use at baseline.

^bModel was adjusted for medication use as time-dependent covariates

^cP interaction was test whether presence of interaction effect between menopause symptoms and number of risk factor.

Table 4 Hormone therapy and risk of HF

	All patients			Symptomatic menopausal cohort patients			Control cohort patient		
	CHR (95% CI)	P-value	aHR (95% CI)	P-value	aHR (95% CI)	P-value	aHR (95% CI)	P-value	
HF	1	1	1	1	1	1	1	1	
Control	1.057(0.923, 1.211)	0.4203	0.932(0.796, 1.092)	0.3822	0.962(0.809, 1.145)	0.6651	0.836(0.535, 1.308)	0.4335	
HT user									

HF, heart failure; HT, hormone therapy. Adjusted for all variables listed in Table 1, comorbidities and medication use were time-dependent covariates.

Discussion

Menopausal symptoms have differential impacts on the risks of CHD and HF

From NHIRD, we cannot identify the menopausal symptoms directly. We tried to approximately estimate the menopausal symptoms by the symptomatic menopausal diagnosis with corresponding medications (Table S1). The results showed that in our study, the top four drugs were hormone therapy, followed by anxiolytic drugs, beta blockers and hypnotics. This finding was suggestive of the major menopausal symptoms such as vasomotor symptoms, hot flashes, anxiety and insomnia in our study group. The main finding of our study clearly pointed out that menopausal symptoms have differential impacts on the risks of CHD and HF (Figure 3). We aimed to provide a potential explanation for this discrepancy, but further trials are needed. This discrepancy is probably owing to women with menopausal symptoms having associated low-grade systemic inflammation status.¹¹ Vascular inflammation underlies the pathogenesis of atherosclerosis. Low-grade inflammation has been shown to be involved in the atherosclerotic process owing to endothelial dysfunction.²⁰ Oestrogen exerts anti-inflammatory effects on the vasculature through different mechanisms such as direct antioxidant effects, generation of nitric oxide, prevention of apoptosis in vascular cells and suppression of cytokines and the renin–angiotensin system.^{21,22} Vascular dysfunction, including arterial stiffness and endothelial dysfunction, is associated with greater frequency and severity of menopausal symptoms across the stages of menopause.¹⁰ Our finding supports the notion that low-grade systemic inflammation alone may trigger atherosclerotic changes in the vasculature.

However, low-grade systemic inflammation (like menopausal symptoms) alone would not increase the risk of HF in postmenopausal women. HF in postmenopausal women mainly presents as HFpEF,^{13,23,24} which is a distinct phenotype—the so-called inflammatory-metabolic phenotype. It is characterized by biomarkers of inflammation and a broad range of adipogenic metabolic and hormonal disorders, accompanied by epicardial adipose tissue expansion and inflammation, which will increase the risk of HFpEF. Systemic inflammation and abnormal fat metabolism can cause inflammation of adipose tissue (if epicardial fat or intramyocardial lipids are involved), which may amplify systemic processes and concentrate them on the myocardium, thereby exacerbating cardiac inflammation and coronary microvascular endothelial dysfunction. As a result, it impairs the distensibility of the left ventricle and causes cardiac fibrosis. These are the characteristics of inflammatory-metabolic HFpEF.²⁴ The above hypotheses have been well reviewed by Packer et al.²⁵ This highlights that HFpEF is a complex and multifactorial pathophysiology, probably systemic, and

Table 5 Subgroup analyses of the risk of HF in symptomatic menopausal and control cohorts

Subgroup	Subjects without MS		Subjects with MS		Compared with control group			
	N	Event	N	Event	cHR (95% CI)	P-value	aHR (95% CI)	P-value
Age, years								
<50	6274	114	6094	100	0.923(0.705,1.207)	0.5572	0.803(0.589,1.096)	0.1675
≥ 50	8066	487	8246	460	0.933(0.822,1.06)	0.2878	0.946(0.816,1.096)	0.4598
ACEI/ARB								
Non-user	13 841	52	13 847	506	0.965(0.855,1.09)	0.5705	0.94(0.815,1.083)	0.3911
User	499	69	493	54	0.791(0.554,1.129)	0.1963	0.76(0.509,1.134)	0.1792
Beta blocker								
Non-user	13 571	530	13 455	479	0.887(0.767,1.025)	0.1032	0.926(0.818,1.047)	0.2192
User	769	71	885	81	0.987(0.718,1.357)	0.9355	1.077(0.738,1.572)	0.6991

ACEI, angiotensin- converting enzyme inhibitors; ARB, angiotensin receptor blockers; HF, heart failure; MS, menopausal symptoms.

clinically heterogeneous and is associated with frequent multiple chronic comorbidities and multiorgan involvement.²⁶ In our study, the inflammatory burden of participants with traditional risk factors like hypertension, diabetes, metabolic syndrome or obesity, among other chronic adipogenic metabolic disorders, outweighed the burden of women with menopausal symptoms alone (low-grade systemic inflammation). Therefore, menopausal symptoms may not increase the risk of HF in postmenopausal women with comorbidities. Our findings underscore the importance of traditional risk factor control among perimenopausal women and highlight the need for intervention strategies to address the inflammatory triggers of HF.

The incidence of CHD was higher than HF over the time

Another interesting question was that why the higher incidence of CHD in symptomatic women did not lead to a higher incidence of HF over the time in this cohort. In our study, the incidence of HF in the symptomatic menopausal cohort was 4.47 per 1000 person-years, and the incidence of CHD was 17.18 per 1000 person-years. Our finding was concordance with the results of Atherosclerosis Risk in Communities (ARIC) study.²⁷ In ARIC study, 5629 postmenopausal women (mean age 56 years) were follow-up, and the median follow-up time was 21.4 years. The incidence of HF according to age at menopause of <45, 45–49, 50–54 and ≥55 years was 10.7, 8.5, 7.3 and 10.7 events per 1000 person-years, respectively; corresponding estimates for CHD were 15.5, 13.8, 11.1 and 13.3 events per 1000 person-years, respectively. The incidence of CHD was higher than HF over the time. To assess whether the observed association was mediated by CHD, these authors further adjusted for interim CHD, defined as CHD that occurred before HF. Additional adjustment for interim CHD did not significantly change the observed associations with the hazard ratio for incident HF. A nice review provided perspective on this issue.²⁸ Data from the

Framingham Heart Study show that coronary artery disease (CAD) contributes differently to the burden of HF in men and women. The population attributable risk (PAR) of CAD-associated HF is 39% in men and only 18% in women.²⁹ Also, Framingham study data shows that hypertension is an antecedent for the vast majority of HF patients in the community. The PAR of HF associated with hypertension was 39% in men and 59% in women. A majority of perimenopausal or postmenopausal women with hypertension or CHD were in the 'pre-HF' phenotype (Stages A and B). Given that hypertension and CHD are the major modifiable risk factors for HF, risk factors intervention may prevent the future burden of HF. Our study highlight sex differences in HF. Hypertension is the leading comorbidity among postmenopausal women in our study and confers the higher risk for developing HF among women than CHD. The above description may explain why the higher incidence of CHD in symptomatic women did not lead to a higher incidence of HF over the time in this cohort.

Raise awareness of menopausal transition and improve health prevention strategies in middle-aged women

The menopausal transition is a period of significant adverse changes in several cardiometabolic risk factors (such as blood lipids, vascular health, metabolic syndrome and visceral obesity). These findings suggest that vasomotor symptoms are biomarkers of impaired cardiometabolic conditions, not just temporary symptoms of menopausal women.³⁰ Furthermore, the timing of the onset of high blood pressure is usually at the beginning of menopause. Symptoms of female hypertension (such as hot flashes and palpitations) are often mistaken for menopause.³¹ Delay diagnosis of hypertension will put women at risk for HF. When women suffering from menopausal symptoms seek medical help, physicians may use this opportunity to raise women's awareness of the significant adverse cardiometabolic health-related changes

associated with menopausal transition. Meanwhile, physicians can monitor blood pressure and detect high blood pressure earlier in middle-aged women and achieve treatment goals. Most women are interested in physician-recommended healthy lifestyle modification and have good compliance with antihypertensive drugs, which enables them to reduce the possibility of future HF events. This prevention-based approach might explain why the incidence of HF in the control cohort is higher than in the symptomatic menopausal cohort for each risk factor burden category.

Symptomatic menopause manifests through various somatic and psychiatric symptoms, including vasomotor symptoms (i.e. hot flashes and night sweats), urogenital symptoms, headaches and joint pain, depressive and anxious mood, sleep disturbance and feelings of panic. Not all symptoms are necessarily related to ovarian ageing and the production of oestradiol and progesterone. There is no correlation between hormone levels and the severity of symptoms.³²

Oestrogen, hormone therapy and HF

Compared with men of the same age, the incidence of HFpEF in postmenopausal women increases sharply, which indicates that there is a close relationship between left ventricular diastolic dysfunction and oestrogen deficiency.³³ Published report indicates that oestrogen deficiency affects early diastole through calcium homeostasis and late diastolic compliance related to cardiac hypertrophy and fibrosis.³⁴ Due to the positive effects of oestrogen on maintaining heart function, oestrogen therapy has clinical implication for diastolic dysfunction. Some studies have shown that hormone therapy users can significantly improve diastolic parameters on echocardiography. In contrast, some studies have shown that healthy postmenopausal women do not improve after short-term (4 weeks or 8 weeks) and long-term (1 year) hormone therapy. The inconsistent results may be due to different routes of administration, different types and doses of oestrogen used and the duration of effective treatment. These findings are summarized in a review article on clinical studies on the role of oestrogen in diastolic function.³³ In our study, the mean duration of hormone therapy was 3.3 ± 3.4 years in the symptomatic menopausal cohort and 1.3 ± 2.3 years in the control cohort. Our findings revealed no differences in the risk of HF between hormone therapy users and non-hormone therapy users, regardless of whether there are menopausal symptoms. We excluded patients with CHD and HF at baseline, and hormone therapy had a neutral effect on the risk of HF (aHR 0.932, $P = 0.3822$, *Table 4*). However, our study is retrospective analysis from NHIRD. Further clinical studies are needed

to clarify the role of oestrogen therapy in the risk of HF in middle-aged women.

For better understanding the medications impact on the risk of HF, we conducted subgroup analyses focusing on with or without using beta blocker, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Our results indicated that above medications had neutral effect on risk of HF in symptomatic menopausal cohort.

Study limitations

The present study has several limitations. First, the NHIRD does not include detailed imaging data related to HF, such as echocardiography and cardiac magnetic resonance imaging. Therefore, we are unable to determine the subtype of HF, nor do we have information on the percentage of HFpEF, the severity of HF (NYHA level) and echocardiographic parameters in HF patients. Second, some information was not provided by the NHIRD, such as menopausal age, smoking history, body mass index, physical activity, blood pressure, inflammatory markers, blood glucose and lipid profiles. These unmeasured covariates could have an impact on the outcome, even after balancing the baseline clinical characteristics with propensity score matching. Third, symptomatic menopausal transition includes various somatic and psychiatric symptoms, but the NHIRD does not identify the symptoms on which gynaecologists base their diagnoses. Furthermore, we could not assess the severity of menopausal symptoms, symptoms possible presentation before menstrual cessation and age at onset of menopause because the data did not contain related clinical parameters. Finally, because most of the population in Taiwan is Han Chinese, the findings of this study may not be generalizable to populations of different ethnicities.

Conclusions

This large-scale longitudinal retrospective cohort study revealed that menopausal symptoms were associated with CHD risk but were not associated with risk of HF. Traditional risk factors rather than menopausal symptoms play important roles in increasing the incidence of HF among middle-aged women.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Approximately estimate the menopausal symptoms by the symptomatic menopausal diagnosis with corresponding medications.

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