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Research article

Effects of insomnia and non-vasomotor menopausal symptoms on coronary heart disease risk: a mendelian randomization study

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ABSTRACT

Background: Previous studies suggested that vasomotor symptoms were associated with an increasing risk of coronary heart diseases (CHD) but not clear with menopausal symptoms other than vasomotor symptoms. Given the heterogeneity and interrelationship among menopausal symptoms, it is not easy to make causal inferences based on observational studies. We performed a Mendelian randomization (MR) to investigate the association of individual non-vasomotor menopausal symptoms and the risk of CHDs.

Methods: A sample of 177,497 British women aged ≥51 years old (average age at menopause) without related cardiovascular diseases from the UK biobank is selected as our study population. Non-vasomotor menopausal symptoms, including anxiety, nervous, insomnia, urinary tract infection, fatigue, and vertigo, were selected as exposures based on the modified Kupperman index. Outcome variable is CHD.

Results: In total, 54, 47, 24, 33, 22, and 81 instrumental variables were selected for anxiety, insomnia, fatigue, vertigo, urinary tract infection and nervous respectively. We conducted MR analyses of menopausal symptoms and CHD. Only insomnia symptoms increased the lifetime risk of CHD with OR 1.394 ($p = 0.0003$). There were no significant causal relationships with CHD and other menopausal symptoms. Insomnia near menopause age (45–50 years) does not increase the risk of CHD. However, postmenopausal (over 51) insomnia increases the risk of CHD.

Conclusion: MR analyses support that among non-vasomotor menopausal symptoms, only insomnia symptoms may increase the lifetime risk of CHD. Insomnia at different ages near menopause has differential impacts on CHD risk.

Abbreviations: MR, Mendelian randomization; CHD, coronary heart disease.

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1. Introduction

As women traverse the menopause transition, they may experience multiple symptoms such as hot flashes and night sweats (ie, vasomotor symptoms), mood changes (eg, depression and anxiety), and sleep and cognitive disturbances, as well as genitourinary and sexual function changes [1]. The prevalence of hot flashes and other menopausal symptoms has been reported to be up to 80% in menopausal women, and it is influenced by various factors, such as age, ethnicity, education, smoking, and mood [2,3]. The incidence of cardiovascular diseases (CVDs) has increased in postmenopausal women [4,5]. Links between many of these symptoms and CVD risk have been found [6–8], but mainly are focusing on vasomotor symptoms. Menopausal symptoms other than vasomotor symptoms are rarely discussed in this topic. In view of the impact of menopausal symptoms on long-term women's health, the discovery of individual menopausal symptoms is essential for early detection and intervention. However, symptoms such as vasomotor symptoms, sleep disturbances, and mood changes are comorbid features during menopause transition and can affect each other [9]. Given the heterogeneity and interrelationship between menopausal symptoms, it is not easy to make causal inferences based on observational studies to determine which menopausal symptoms are associated with CVD risk. Menopausal symptoms other than vasomotor symptoms, including anxiety, nervous, insomnia, urinary tract infection, fatigue, and vertigo, were selected as exposures based on the modified Kupperman index (mKMI) [10] and clinical practice. The mKMI combines the patient's perspective and physician's evaluation. It aimed to evaluate vasomotor, somatic, psychiatric and uro-genital symptoms.

Mendelian randomization (MR) is an epidemiological technique that uses genetic variants as instrumental variables for an exposure to distinguish correlation from causation in observational data [11]. The associations obtained from MR analysis are unlikely to be biased by confounding, because genetic variants are randomly assigned at conception, so this trait is usually unrelated to other traits. To overcome above mentioned limitation, MR by using UK biobank database to explore the causal relationship between menopausal symptoms other than vasomotor symptoms and future CHD events is suitable.

Furthermore, UK biobank with huge amount genetic variants using MR approach is suitable to make casual inference on risk factors

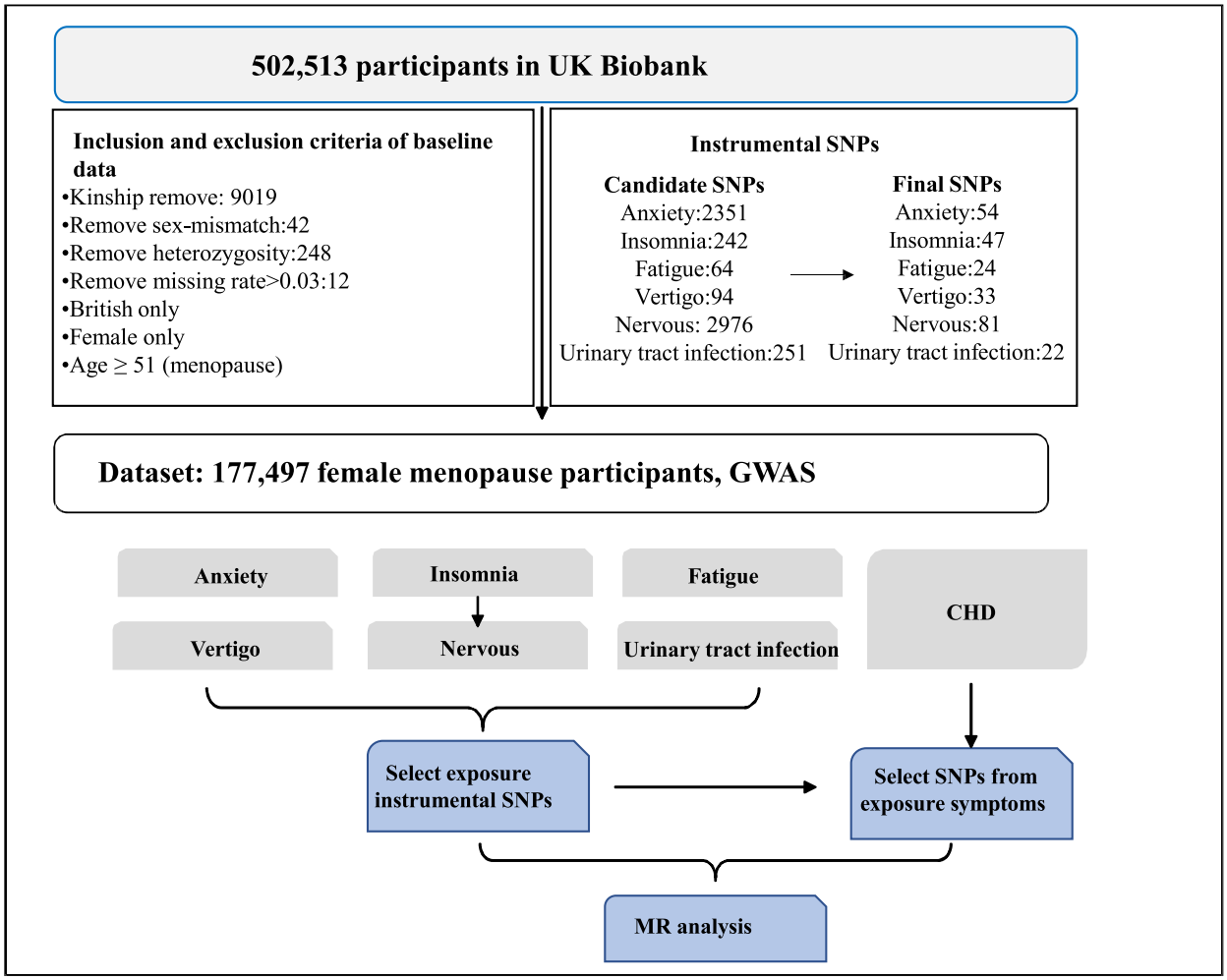

Fig. 1. Study flow chart.

with small to moderate impact [12]. However, in UK biobank there was no approximate questionnaire about menopausal vasomotor symptoms. We select symptoms except vasomotor symptoms, including anxiety, nervous, insomnia, urinary tract infection, fatigue and vertigo for MR study. Those above symptoms have clear definition in UK biobank questionnaire.

After comprehensively review previous MR evidence for anxiety [13], nervous [14], insomnia [15] associated with CHD, the results were mixed, most of which focused on general population without gender specific. No MR studies have assessed associations of urinary tract infection, fatigue and vertigo with CHD. However, somatic, psychiatric and uro-genital symptoms are also common symptoms of menopause. Whether these symptoms increase the risk of CHD is unclear, but few studies discuss the association with CHD using MR methods. The aim of the study was to explore which menopausal related symptoms other than vasomotor symptoms will increase the risk of CHD by using UK biobank database with MR approach. In addition, we also want to know whether these symptoms affect the risk of coronary heart disease during or after the menopausal transition period.

2. Material and methods

Ethical statement

The UK biobank is an open access resource that researchers can apply to use. This study was conducted using UK biobank Research under application number 46789. The research included in the GWAS used has been approved by the Institute Review Board of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, with the approval number AS-IRB01-19004 and Changhua Christian Hospital in Taiwan, with the approval number CCH-IRB-211029. All methods were carried out in accordance with relevant guidelines and regulations.

2.1. UK biobank population and study design

The UK biobank is an ongoing prospective population-based cohort study that enrolled >500,000 volunteers 40–69 years of age from 2006 to 2010 in the UK [12]. At the time of recruitment, participants gave informed consent to participate and were followed up. Overall, 503,317 participants agreed to join the study cohort and visited the assessment center. The total number of participants in the UK biobank is 502,513. The number of female participants in the UK biobank is 273,377. We only enrolled 240,248 British female participants. The number of participants excluded from the kinship inference process is 9019. The number of British women aged ≥51 (the average age of menopause for British women [16]) is 177,797. Among them, PLINK 1.9 check-sex routine identified 42 with sex-mismatch or sex chromosome karyotypes putatively different from XX or XY. The heterozygosity was tested by plink-het, and 248 with deviations of more than 6 standard deviation were identified as outliers, and 12 subjects with missing rate >0.03 were identified by plink-missing. After exclusion the above, sample of 177,497 subjects were used as our study population. A flowchart of the cohort selection process is presented in Fig. 1.

3. Exposure and outcome

We choose most commonly related symptoms during menopausal transition according to mKMI and clinical practice. We select symptoms except vasomotor symptoms, including anxiety/nervousness, insomnia, urinary tract infection, fatigue and vertigo for MR study. Outcome was CHD.

Anxiety was defined as “Seen doctor (GP) for nerves, anxiety, tension or depression” (data field #2090).

Insomnia was defined as “Trouble falling or staying asleep, or sleeping too much” (data field #1200).

Fatigue was defined as “Recent feelings of tiredness or low energy” (data field #20519).

Vertigo was defined as “non-cancer illnesses that self-reported as vertigo” (data field #20002).

Urinary tract infection was defined as **s**elf-reported as “urinary tract infection/kidney infection” (data field #20002, #41202, #41204).

Nervous was defined as “Nervous feelings” (data field #1970).

Coronary heart disease was defined as fatal or nonfatal myocardial infarction (MI) cases, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG).

In UK biobank self-reported data, cases were defined as having had a heart attack diagnosed by a doctor (data field #6150); “non-cancer illnesses that self-reported as heart attack” (data field #20002); or self-reported operation including PTCA, CABG, or triple heart bypass (data field #20004). In HES hospital episodes data and death registry data, MI was defined as hospital admission or cause of death due to ICD-9410 to 412, or ICD-10 I21 to I24 or I25.2.

3.1. Instrumental variables in MR

First, we conducted a genome-wide association analysis in the UK biobank cohort to obtain single nucleotide polymorphisms (SNPs) that were significantly associated with exposure. Using imputation genotype files, info score >0.8, minor allele frequency >0.01, deletion rate <0.05, Hardy-Weinberg equilibrium $P < 1 \times 10^{-7}$. By using the logistic regression of the Plink and Plink2 software in Linux with age being adjusted, the effects of the instrumental SNPs are obtained at the relaxed significance threshold ($P < 5 \times 10^{-5}$). To ensure the independence of SNPs, we use the R function “clump_data” of the “TwoSampleMR” package to prune these SNPs through linkage disequilibrium ($R^2 < 0.001$). Then, we excluded the SNPs outliers by using the MR-Egger method to control the

unknown pleiotropic SNPs. To consolidate any significant finding, we conducted additional MR analysis using independent set of instrumental SNPs obtained from our GWAS to cross-validate the results.

3.2. Statistical analysis

We used the inverse-variance weighted model with random-effects was employed as the statistical analysis of MR. Ratio estimates are calculated for each SNP using the formula: Ratio = beta coefficient for the SNP-outcome association/beta coefficient for the SNP-exposure association. These estimates are then combined in a random-effects inverse-variance weighted meta-analysis. Estimates from this method have the highest precision. We use the Q statistics and MR-Egger outlier test to detect the invalid instrumental SNPs. The Q larger than its degrees of freedom (number of SNPs minus 1) provides evidence for heterogeneity and invalid instruments such as pleiotropy [17]. In the analysis, we did not find any pleiotropy or outlier SNPs, so we used the inverse variance weighted (IVW) method with the highest precision in the statistical aspect. The results by Weighted Median and MR-Egger methods were also listed as sensitivity analyses.

4. Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the UK biobank repository [https://www.ukbiobank.ac.uk/resources].

5. Results

5.1. The characteristics of participants

The age distribution in different menopausal symptoms categories, and habitual variables of 177,497 British women aged ≥51 is shown in Table 1. The average age is 60.7, while there is no significant age difference between the symptoms and non-symptoms groups except urinary tract infection. Age is also not associated the smoking status; however, current alcohol drinkers are younger than the non-drinkers. Sample size of each menopausal symptom and subsequent CHD results are presented in Table 2. The number of legitimate genetic variants used as instrumental variables in MR analyses for anxiety, insomnia, fatigue, vertigo, urinary tract infection and nervous are 54, 47, 24, 33, 22, and 81 respectively. These SNPs were not horizontal pleiotropic and we also ruled out the SNP outliers (unknown pleiotropic SNPs) through the MR-Egger method. The coding of these symptoms and the diagnoses of horizontal

Table 1
Age distribution in different menopausal symptoms categories and habitual variables.

	Age mean	Age median	Std of Age	Q1, Q3
Anxiety				
Yes	60.28	61	5.184	56, 64
No	60.95	61	5.307	57, 65
Insomnia				
Yes	60.61	61	5.215	56, 65
No	60.71	61	5.295	56, 65
Fatigue				
Yes	59.63	60	5.185	55, 64
No	59.8	60	4.98	56, 64
Vertigo				
Yes	60.78	61	5.22	57, 65
No	60.67	61	5.268	56, 65
Urinary tract infection				
Yes	62.03	63	5.284	58, 66
No	60.6	61	5.258	56, 65
Nervous				
Yes	60.63	61	5.211	56, 65
No	60.67	61	5.287	56, 65
CAD				
Yes	63.20	64	4.957	60, 67
No	60.61	61	5.26	56, 65
Smoking				
1 Non-Smoking	61.07	62	5.083	57, 65
2 Smoke (once/twice)	60.88	61	5.218	57, 65
3 Smoke (Sometimes)	60.53	61	5.274	56, 65
4 Smoke (Almost)	60.59	61	5.348	56, 65
Drink				
0 No drinking	62.38	63	5.124	59, 67
1 Drink (Previous)	61.04	61	5.242	57, 65
2 Drink (Current)	60.57	61	5.259	56, 65
Total (177,497)	60.67	61	5.268	56, 65

Table 2
Sample size of each menopausal symptom and subsequent CHD results.

	CAD	Non-CAD	Total[a]	p-value
Sample size	4043 (2.27%)	173,454	177,497	
Anxiety				
Yes	1929 (2.65%)	70,822	72,751	
No	2079 (2.01%)	101,333	103,412	<2.2e-16
Insomnia				
Yes	1733 (2.78%)	60,456	62,189	
No	2309 (2%)	112,922	115,231	<2.2e-16
Fatigue				
Yes	461 (1.56%)	29,051	29,512	
No	247 (0.87%)	28,140	28,387	4.859e-14
Vertigo				
Yes	9 (1.92%)	459	468	
No	4034 (2.27%)	172,995	177,029	0.7189
urinary tract infection				
Yes	539 (6.25%)	8077	8616	
No	3504 (2.07%)	165,377	168,881	<2.2e-16
Nervous				
Yes	1118 (2.35%)	46,424	47,542	
No	2808 (2.25%)	121,747	124,555	0.2343

[a] Non-reply rates, anxiety: 0.7%, insomnia: 0.04% fatigue: 67.38%, nervous: 3%.

pleiotropy for each symptom is shown in Table 3.

5.2. Mendelian randomization results for menopausal symptoms on probable life time CHD risk

In a MR analysis of menopausal symptoms and CHD, IVW method (Table 4) shows that the risk of CHD was increased 1.0717 times ($p = 0.444$) when menopausal symptom was anxiety; increased 1.394 times ($p = 0.0003$) when symptoms was insomnia; increased 1.097 times ($p = 0.271$) when symptoms was fatigue; increased 1.004 times ($p = 0.79$) when symptom was vertigo; increased 1.0251 times ($p = 0.714$) when symptom was urinary tract infection and increased 0.9023 times ($p = 0.13$) when symptom was nervous. In sensitivity analysis, weighted median method also indicates a significant causal relationship between CHD and menopausal symptoms of insomnia. The results of weighted median and MR-Egger are consistent with those of IVW, except MR-Egger for insomnia. There were no significant causal relationships with CHD and other menopausal symptoms. All the F-statistics >10, suggest strong IVs for each symptom. All the Q statistics are less than its degrees of freedom (number of SNPs minus 1), provides no evidence for heterogeneity or pleiotropy.

For cross-validation, Table 5 shows the results by using independent set of instrumental SNPs obtained from GWAS by Jansen et al. (2019) [18] with p-value $<10^{-5}$. Both results are consistent with each other.

5.3. Insomnia symptoms at different ages before/after menopause has differential impacts on CHD risk

We want to know whether insomnia at different ages approaching to menopause have the same contribution to the risk of CHD. We used the same selection criteria for instrumental variables in MR except different ages in UK biobank to evaluate the age-modified

Table 3
Coding of each menopausal symptom and the corresponding number of legitimate SNPs as instrumental variables identified from UKB.

Menopausal symptom	Definition and coding	No of IV identified	Intercept[a]	SE	p-value	Pleiotropy
Anxiety	Seen doctor (GP) for nerves, anxiety, tension or depression.	54	0.0031	0.0122	0.7992	None
coding	1: yes, 0: no					
Insomnia	Sleeplessness/insomnia	47	0.0074	0.0116	0.5262	None
coding	1: Usually, 0: Sometimes/Never/rarely					
Fatigue	Recent feelings of tiredness or low energy	24	−0.0276	0.0165	0.1085	None
coding	1: not at all, 0: several days or more					
Vertigo	Vertigo (Non-cancer illness code, self-reported,Answer = 1500)	33	−0.0396	0.0464	0.4002	None
coding	1: Answer 0: No Answer					
Urinary tract infection	Urinary tract infection/kidney infection Urinary tract infection, site not specified	22	0.0143	0.0163	0.3905	None
coding	1: Answer, 0: No Answer					
Nervous	Nervous feelings	81	−0.0007	0.0100	0.9366	None
coding	1: Yes, 0: No					

[a] Diagnoses of horizontal pleiotropy of SNPs for corresponding symptoms by the inference on intercept estimated from MR-Egger.

Table 4
Mendelian randomization results for menopausal symptoms on probable life time CHD risk after adjustment of age.

Menopausal symptoms	Method	OR	95%CI	p-value	F-stat*2	Q-stat*3	P-value (heterogeneity)	nsnp	ncase
Anxiety	IVW*1	1.0717	(0.8973, 2.2835)	0.4443	24.394			54	72,865
	MR Egger	1.0041	(0.5904, 1.7070)	0.9879		31.02	0.993		
	Weighted median	1.1544	(0.9065, 1.4701)	0.2440					
Insomnia	IVW	1.3942	(1.1610, 1.6744)	0.0003	25.051			47	62,292
	MR Egger	1.2043	(0.7412, 1.9566)	0.4566		35.98	0.855		
	Weighted median	1.4080	(1.0794, 1.8366)	0.0116					
Fatigue	IVW	1.0972	(0.9301, 1.2944)	0.2709	21.402			24	29,556
	MR Egger	1.4981	(1.0036, 2.2361)	0.0605		21.36	0.559		
	Weighted median	1.0925	(0.8742, 1.3654)	0.4364					
Vertigo	IVW	1.0043	(0.9726, 1.0370)	0.7904	21.734			33	468
	MR Egger	0.9611	(0.8774, 1.0527)	0.4002		27.42	0.698		
	Weighted median	1.0114	(0.9654, 1.0596)	0.6315					
Urinary tract infection	IVW	1.0251	(0.8976, 1.1706)	0.7140	22.578			22	8636
	MR Egger	0.9156	(0.6886, 1.2176)	0.5514		11.47	0.953		
	Weighted median	1.1268	(0.9381, 1.3533)	0.2015					
Nervous	IVW	0.9023	(0.7900, 1.0306)	0.1298	23.501			81	47,621
	MR Egger	0.9170	(0.6030, 1.3946)	0.6867		73.75	0.675		
	Weighted median	0.8836	(0.7287, 1.0715)	0.2085					

*1 IVW: Inverse Variance Weighted method. *2 F-statistics >10 suggest strong IVs. *3 Q statistics: if larger than its degrees of freedom (number of SNPs minus 1) provides evidence for heterogeneity.

Table 5
An MR analysis on insomnia using independent set of instrumental SNPs obtained from GWAS by Jansen et al. (2019) with p-value $<10^{-5}$.

		beta	se	p-value	F-stat	nsnp
Insomnia	IVW	0.3275	0.1075	0.0023	18.601	59
	MR-egger	0.1549	0.2944	0.6007		
	Weighted median	0.3542	0.1523	0.0200		

effect of insomnia on risk of CHD. Our research results show that insomnia $\geq$ 51 years old has a significant effect on increasing the risk of CHD, while insomnia $\geq$ 45 or $\geq$ 48 years old does not (Table 6).

6. Discussion

6.1. The importance of insomnia among non-vasomotor symptoms on CHD risk in menopausal women

The main finding of our study is that we identify insomnia as a significant risk factor for coronary heart disease in women $\geq$ 51 years old and an important menopausal symptom. Data from the Women's Health Initiative of the National Institutes of Health showed that in 86,329 postmenopausal women, self-reported insomnia was associated with an increased risk of coronary heart disease (CHD) or cardiovascular disease within 10 years [19]. Mounting evidence points to a potential link between insomnia and cardiovascular disease [20]. The prevalence rates of self-report sleep difficulties ranging between 40% and 56% in perimenopause and postmenopause, compared to premenopausal women in the late reproductive stage, who have rates of 31% [21]. The presence of self-reported hot flashes is consistently associated with poorer self-reported sleep quality and chronic insomnia [21,22], which suggests that women associate hot flashes with waking up at night. Studies further supporting hot flashes as the cause of poor sleep have shown that effective treatment of hot flashes with hormone therapy is related to improving sleep quality [23]. Sleep problems are multifactorial and are closely related to hot flashes and mood disorders, as well as other factors related to middle-aged aging, including stress, poor health and chronic pain [24]. Since insomnia usually coexists with mood disorders and cardiopulmonary diseases, it is difficult to determine causality from observational data. Previous studies have suggested that insomnia is related to cardiovascular disease, and have been criticized for failing to adequately control confounding factors such as depression and anxiety. This limits the ability to quantify the

Table 6
Mendelian randomization results for insomnia symptoms at different ages approaching menopause on probable life time CHD risk.

Menopausal symptoms	Range of Age	IVW*		Q** statistics		
		OR and 95%CI	p-value	Heterogeneity	p-value	no.snp
Insomnia	≥45	1.118 (0.881,1.417)	0.357	14.998	0.378	15
Insomnia	≥48	1.179 (0.965,1.441)	0.1059	16.919	0.528	19
Insomnia	≥51	1.394 (1.161,1.674)	0.0003	35.98	0.8554	47

IVW: Inverse Variance Weighted method. **Q statistics: larger than its degrees of freedom (number of SNPs minus 1) provides evidence for heterogeneity.

impact of insomnia and also limits the ability to determine whether insomnia is a risk factor for cardiovascular disease [25].

Our findings provide robust evidence that menopausal women with insomnia symptoms may increase the risk of coronary heart disease regardless of whether they have vasomotor symptoms or not. Physician can recommend appropriate treatment options, including medications, cognitive behavioral therapy and lifestyle changes that may improve sleep. Some people advocate listing sleep disorders as the tenth potentially modifiable cardiovascular risk factor [25]. A recent sleep study using the "epigenetic clock" method evaluated more than 2000 women in the Women's Health Initiative and found that women who woke up repeatedly throughout the night, sleep restlessly, had difficulty falling asleep, had difficulty falling asleep again and waking up too early in the morning may be biological older than women of the same chronological age [26]. Their study shows that menopause and insomnia may accelerate aging epigenetically. This may increase the risk of women suffering from aging-related diseases such as CHD.

6.2. Insomnia in different age groups have differential impact on the risks of CHD

Menopausal transition is characterized by an increased prevalence of sleep disorders and insomnia, which occurs in 40–60% of women. Women may be more susceptible to the negative cardiometabolic consequences of poor sleep, especially after menopause [27,28]. The insomnia phenotype appears when women are approaching menopause, mainly between the ages of 48–50. We want to know whether insomnia at different ages approaching to menopause have the same contribution to the risk of coronary heart disease. Our research results show that insomnia $\geq$ 51 years old has a significant effect on increasing the risk of CHD, while insomnia $\geq$ 45 or $\geq$ 48 years old does not. This may indicate that the effects of insomnia from the age of 45–50 years do not accumulate the risk of coronary heart disease. One possible explanation may be sympathetic nerve activity. Sympathetic nerve activity is disproportionately affected by age and gender [29]. Specifically, compared with age-matched men, women tend to have lower resting sympathetic nerve activity in the early life (20–39 years), roughly similar levels in middle age (40–49 years), but sympathetic nerve activity rises significantly at older ages. Compared with women in menopausal transition (aged between 48 and 50 years), this sharp increase in postmenopausal sympathetic activity may explain why insomnia in postmenopausal women (age $\geq$ 51 years) was associated with higher CHD risk. The underlying mechanism is unclear and need further investigation.

Table 6 shows an age-insomnia interaction effect on CHD; however, the effect depends on the way of stratification on age. This may raise an issue of selection-induced collider bias [30], that is, the collider variable controlled/stratified been influenced by both exposure (insomnia) and outcome (CHD) [31]. Since age may influence insomnia and CHD, but not the other way around, it is more of a confounder rather than collider.

6.3. Other MR studies in insomnia

When reviewing the previous MR study conducted using the biobank database [15], our results are also consistent with their findings, indicating that insomnia is a risk factor for CHD. However, the magnitude of these estimates in our study is larger. In Yuan's study [15], the odds ratio of CHD was 1.19; in our study, the OR of CHD was 1.275. The reason behind the difference in effect size may be the gender difference in the association between insomnia and CHD risk factors. In our study, we only focused on postmenopausal women, while another MR study included both sexes. Our findings indicate that middle-aged women seem to be more susceptible to the impact of insomnia on the risk of CHD.

6.4. Advantages of MR studies

Nervous and anxiety are two common health problems among middle-aged women. The risk of these two mental illness occurrences has been reported to increase in women during the perimenopausal and postmenopausal stages [32,33]. The prevalence of anxiety symptoms among peri- and postmenopausal women is 7%–25% [33,34]. Furthermore, depression/anxiety or mood symptoms can make people susceptible to other physical illnesses, and physical illnesses can cause depression or anxiety or mood symptoms, and usually exacerbate distress. Multivariable analysis showed that poor health status, trouble falling asleep, and early awakening were independently associated with symptoms of anxiety [35]. Therefore, these conditions are suitable using MR for preventing confounding and reverse causality. Our results indicated that nervous and anxiety will not increase the risk of CHD. In term of fatigue, vertigo and urinary tract infection symptoms did not increase the risk of CHD among perimenopausal transition and post menopause. Therefore, our results provide robust data about non-vasomotor menopausal symptoms and risk of CHD.

6.5. Significance of the study and clinical implications

Menopausal symptoms are heterogeneous, with a set of individual symptoms. Each symptom has varying degrees of severity and interactions among individual symptoms. Our MR study highlights the importance of sleep health during the menopausal transition and post menopause in predicting coronary heart disease risk in middle-aged women. In terms of clinical implications, we summarize the following points.

1. Using sleep as a metric of cardiovascular health, like other health behaviors, can enhance CVD prevention efforts in women's health.
2. Insomnia is not only a bothersome menopause symptom, it's also a risk factor. Awareness campaigns for widespread screening for sleep disturbances in perimenopausal women should be a priority.

3. Non-pharmacological treatment, such as cognitive behavior therapy, may provide alternative therapy.
4. Pharmacotherapy of insomnia is controversial in cardiovascular disease prevention; our study may provide clues to new pharmacological studies elucidating CVD interactions, but more evidence is needed.

7. Limitations

There were some limitations in our study. First, analysis in our study included here (UK biobank) was restricted to women of European ancestry. Further work is required to investigate whether these findings translate to women in other ancestry groups. It is known that the participants of UK biobank are more likely to be "healthier" than the general population. Second, in the UK biobank, the age of the participants is between 40 and 69 years old, and our results may not apply to people over 70 years old. Third, we do not know the actual menopausal age in our study. We use the average menopausal age reported in the literature as the menopausal age in this study. Nonetheless, valid inference on exposure-disease relationships may still be generalizable despite this selection bias [36].

In this study, considering that the dataset with CHD outcome is the complete one, and the data with exposure menopause is only a subset, we conducted the analysis using two-sample MR. The simulation study by Pierce and Burgess (2013) [37] shows that the impact of using only partial exposure data and two-sample ratio estimate often having negligible difference in comparison with a traditional complete-data analysis, as long as the size of the subset is enough to achieve maximum power depends on IV strength. Minelli et al. (2021) also demonstrated that two-sample MR methods can be safely used for one-sample MR performed within large biobanks [38].

In sensitivity analysis, the results of weighted median method and MR-Egger are consistent with those of IVW, except for insomnia, where both IVW and median-based method suggest a significant causal relationship with CHD but not MR-Egger for insomnia. This is coincided with the simulation by Bowden et al. (2016) [39] where MR-Egger usually have lower power than the other two.

8. Conclusion

MR analyses support that among menopausal symptoms other than vasomotor symptoms, only insomnia symptoms will increase the lifetime risk of CHD. Further analyses of different age groups approaching menopause show that insomnia will affect the risk of CHD after menopausal transition. However, insomnia at the age of 45 or 48 does not increase the risk of coronary heart disease.

Declarations

Author contribution statement

Ching-Hui Huang and Ie-Bin Lian: Conceived and designed the experiments; Wrote the paper. Jia Jyun Sie: Analyzed and interpreted the data; Wrote the paper.Chia-Chu Chang, Cathy S. J. Fann: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

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CRediT author statement

Iebin Lian: Conceptualization, Supervision, Reviewing and Editing Jiajuan Sie: Methodology, Software, Reviewing. Chia-Chu Chang: Validation, Investigation, Editing Cathy SJ Fann: Data curation, Writing- Original draft preparation. Ching-Hui Huang: Conceptualization, Writing- Reviewing and Editing.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e13569.

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