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Interaction effects between insomnia and depression on risk of out-of-hospital cardiac arrest: Multi-center study

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Abstract

Background

Insomnia and depression have been known to be risk factors of several diseases, including coronary heart disease. We hypothesized that insomnia affects the out-of-hospital cardiac arrest (OHCA) incidence, and these effects may vary depending on whether it is accompanied by depression. This study aimed to determine the association between insomnia and OHCA incidence and whether the effect of insomnia is influenced by depression.

Methods

This prospective multicenter case-control study was performed using Phase II Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiology Surveillance (CAPTURES-II) project database for OHCA cases and community-based controls in Korea. The main exposure was history of insomnia. We conducted conditional logistic regression analysis to estimate the effect of insomnia on the risk of OHCA incidence and performed interaction analysis between insomnia and depression. Finally, subgroup analysis was conducted in the patients with insomnia.

Results

Insomnia was not associated with increased OHCA risk (0.95 [0.64–1.40]). In the interaction analysis, insomnia interacted with depression on OHCA incidence in the young population. Insomnia was associated with significantly higher odds of OHCA incidence (3.65 [1.29–10.33]) in patients with depression than in those without depression (0.84 [0.59–1.17]). In the subgroup analysis, depression increased OHCA incidence only in patients who were not taking insomnia medication (3.66 [1.15–11.66]).

Conclusion

Insomnia with depression is a risk factor for OHCA in the young population. This trend was maintained only in the population not consuming insomnia medication. Early and active medical intervention for patients with insomnia may contribute to lowering the risk of OHCA.

Introduction

Sudden cardiac death (SCD) is a major public health burden because of its high incidence and low survival rates. The average global incidence of SCD among adults is approximately 55 per 100,000 person-years and 97.1 per 100,000 population in USA [1]. Survival to discharge rate is lower in Asia (4.5%) than that in North America (7.7%) and Europe (11.7%) [2]. Despite advances in resuscitation technology and post-resuscitation care for SCD patients, survival outcomes after SCD remain poor [3–5].

The approach to SCD risk stratification is difficult. Recent studies suggest that there are several unrecognized variables that directly affect cardiac function and the occurrence of arrhythmias related to the risk of SCD; however, the risk of SCD is also associated with classical factors, such as hypertension, diabetes mellitus, and dyslipidemia [6, 7].

Insomnia, the most common sleep disorder, is characterized by difficulty initiating and maintaining sleep. It may also take the form of early-morning awakening in which the individual awakens several hours early and is unable to resume sleeping [8]. The duration and continuity of sleep is associated with homeostasis of cardiovascular, metabolic, and immune systems, and insomnia has been shown to adversely influence metabolism and endocrine function, including altering the hypothalamic-pituitary-adrenal axis and elevating biomarkers of chronic inflammation [9–11]. Numerous previous studies have shown that insomnia is associated with an increased coronary heart disease and that it influences cardiovascular mortality; however, results to date have been inconsistent [12–14]

Depression, which is often accompanied with insomnia, not only increases the risk of a new event of heart disease but also increases the risk of recurrent events in patients with heart disease through several biological pathways [15, 16].

Insomnia and depression are commonly comorbid and are associated with significant distress, daytime fatigue, and increased likelihood of day-time sleep, in addition to pathological effects [17, 18]. Consequently, it can impair an individual's ability to adapt and respond to illness [19, 20].

Therefore, it is important to understand whether insomnia and depression may by associated with OHCA risk both independently and in conjunction. We hypothesized that insomnia affects the risk of OHCA through several processes and that these effects may vary depending on whether or not depression is present. The purpose of this study, therefore, was to determine the association of insomnia with the risk of OHCA and identify if its effect is influenced by depression.

Methods

Study design, setting, and data source

This study was performed using Phase II Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAPTURES-II) project database in Korea.

The CAPTURES project is a prospective, multi-center, case-control study, which aims to identify risk factors for OHCA and evaluate prognostic factors with long-term follow-up. Phase I CAPTURES was performed in 27 hospitals from January to December 2014. A detailed description of Phase I CAPTURES has been previously reported [21].

The CAPTURES-II project was a prospective case-control study conducted at 17 university hospitals from September 2017 to December 2020 [21, 22]. The CAPTURES-II was a hospital-based open-cohort study, which included patients who suffered OHCA with a presumed cardiac etiology, were transported to the participating emergency department (ED) by emergency medical services (EMS) and identified by the emergency physicians, and matched community-based controls. The CAPTURES-II registry included face-to-face interview for demographics, comorbidities assessment, health behaviors monitoring, medical record review including laboratory test results, short- and long-term follow-ups (1 month, 6 months, and 12 months after hospital discharge), and blood sample collection for biomarker evaluation. For community-based controls, face-to-face interview and medical record review were conducted to obtain the same information concerning OHCA, and blood sample collection was performed. The data collected from all participating hospitals were transferred to the Quality Management Committee (QMC), where quality control and statistical analysis were performed. The QMC provided feedback to research coordinators on data quality control through monthly meetings. If the research coordinator was unable to define a coding element, they consulted the emergency physicians in the QMC for clarification.

The study was approved by the ethics committees in all participating institutions. In compliance with the Declaration of Helsinki, all participants, or their proxies, provided a written informed consent prior to their participation in the study. This study is registered at Clinical-Trials.gov (NCT03700203).

Study population

Cases were defined as adult (aged over 18 years) EMS-treated OHCA patients who had a presumed cardiac etiology and visited participating hospitals from September 2017 to December 2020.

CAPTURES II control recruitment was conducted by two participating hospitals (one metropolitan and one non-metropolitan) by cooperating with various community centers and public health centers. Community-based controls who were voluntary applications were recruited as control group. The controls were randomly matched within the strata, including age (10-year intervals), sex, and type of residence (metropolitan vs. urban or rural), with a 1:1 ratio of controls to cases.

Variables and measurements

The main exposure was history of insomnia as measured via face-to-face interviews with the patients and community-based controls or their families (for cases). Insomnia history was defined as a positive case of answering "yes" to the question "Have you ever been diagnosed with insomnia?" Depression history was defined in the same way.

The CAPTURES-II registry used the same questionnaire for cases and controls. We collected information on patient demographics (age, sex, residence area [metropolis vs. urban or rural], insurance, education level), comorbidities (hypertension, diabetes, dyslipidemia, stroke), health behaviors (smoking, alcohol, coffee, physical activity), and sleep-related variables, as well as obesity, work type, sleeping medication, snoring, and sleep apnea. Whether or not comorbidities and sleep-related history were diagnosed by a doctor was investigated. Alcohol drinking was defined as heavy alcohol drinking when men drank more than 15 drinks per

week and women drank more than 8 drinks per week and physical activity was defined as vigorous when exercising to the extent of sweating at least once a week, and moderate when exercising less than once a week [23, 24].

Statistical analysis

Demographic findings of the OHCA case group and community-based control group were described. Categorical variables were analyzed using the chi-square test, and continuous variables with normal distribution were analyzed using the t-test. Case-control matching was performed based on age, sex, and residence (metropolis vs. urban or rural). For the case-control dataset, conditional logistic regression analysis was conducted to estimate the effect of insomnia and depression on the risk of OHCA incidence and to calculate the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) after adjusting for potential confounders identified in directed acyclic graph models. We also conducted interaction analysis between history of insomnia and history of depression according to age group. Finally, subgroup analysis was performed in the patients with insomnia. In subgroup analysis, we conducted interaction analysis between history of depression and insomnia medication. All variables in the final model were assessed for multicollinearity, which was not detected in this analysis.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All p-values were two tailed, and p<0.05 was considered statistically significant.

Ethics statements

This study was approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No. 2017–285) and the requirement for informed consent was waived due to the retrospective nature of this study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

Main results

A total of 1014 OHCA cases and 1014 community-based controls were included in this analysis.

The characteristics of the OHCA cases and community-based controls are shown in Table 1. And, the characteristics according to the history of insomnia and depression are reported Tables 2 and 3.

The results of conditional logistic regression models, including AORs (95% CIs), for OHCA with history of insomnia and depression are shown in Table 4. Insomnia was not associated with increased OHCA risk (AOR [95% CI]: 0.95 [0.64–1.40]). Depression also was not a risk factor of OHCA (0.86 [0.67–1.10]).

Interaction analysis

We added an interaction term between history of insomnia and depression to the fully adjusted model. The AORs assessing the statistical interaction on OHCA risk from the conditional logistic regression analysis are shown in Table 5. Insomnia interacted with depression on OHCA incidence in the young population (0.84 [0.59–1.17] for patients without depression, 3.65 [1.29–10.33] for patients with depression, p for interaction <0.01). In subgroup analysis, history of depression was associated with significantly higher odds of OHCA incidence for patients taking insomnia medication (3.66 [1.15–11.66]) than those not taking insomnia medication (1.05 [0.99–12.22]) (p for interaction <0.01).

Table 1. Characteristics of the out-of-hospital cardiac arrest case group and age-, sex-, and urbanization level-matched control group.

Variables	All	OHCA case	Community control	
	N (%)	N (%)	N (%)	p-value
All	2,028 (100.0)	1,014 (100.0)	1,014 (100.0)	
Age				1.00
18–29	38 (1.9)	19 (1.9)	19 (1.9)	
30–39	114 (5.6)	57 (5.6)	57 (5.6)	
40–49	276 (13.6)	138 (13.6)	138 (13.6)	
50–59	512 (25.2)	256 (25.2)	256 (25.2)	
60–69	544 (26.8)	272 (26.8)	272 (26.8)	
70–120	544 (26.8)	272 (26.8)	272 (26.8)	
Gender, female	554 (27.3)	277 (27.3)	277 (27.3)	1.00
Metropolis, yes	1,028 (50.7)	514 (50.7)	514 (50.7)	1.00
Comorbidity				
Hypertension	823 (40.6)	454 (44.8)	369 (36.4)	<0.01
Diabetes mellitus	411 (20.3)	274 (27.0)	137 (13.5)	<0.01
Dyslipidemia	365 (18.0)	130 (12.8)	235 (23.2)	<0.01
Stroke	115 (5.7)	85 (8.4)	30 (3.0)	<0.01
Insurance, medical aid	210 (10.4)	110 (10.8)	100 (9.9)	0.47
Education level, high	646 (31.9)	253 (25.0)	393 (38.8)	<0.01
Obesity, yes	146 (7.2)	35 (3.5)	111 (10.9)	<0.01
Married, yes	1,544 (76.1)	705 (69.5)	839 (82.7)	<0.01
Work type				
Night work	362 (17.9)	100 (9.9)	262 (25.8)	<0.01
Shift work	178 (8.8)	32 (3.2)	146 (14.4)	<0.01
Physical activity				<0.01
Vigorous	365 (18.0)	115 (11.3)	250 (24.7)	
Moderate	365 (18.0)	115 (11.3)	250 (24.7)	
No	549 (27.1)	159 (15.7)	390 (38.5)	
Coffee, yes	697 (34.4)	202 (19.9)	495 (48.8)	<0.01
Smoking				<0.01
Current smoker	536 (26.4)	343 (33.8)	193 (19.0)	
Ex-smoker	597 (29.4)	252 (24.9)	345 (34.0)	
Non-smoker	895 (44.1)	419 (41.3)	476 (46.9)	
Alcohol drinking				<0.01
Heavy	617 (30.4)	309 (30.5)	308 (30.4)	
Moderate	661 (32.6)	246 (24.3)	415 (40.9)	
No	750 (37.0)	459 (45.3)	291 (28.7)	
Sleeping pill, yes	95 (4.7)	60 (5.9)	35 (3.5)	<0.01
Sleep disorder				
Insomnia	543 (26.8)	272 (26.8)	271 (26.7)	0.96
Snoring	1,073 (52.9)	493 (48.6)	580 (57.2)	<0.01
Sleep apnea	350 (17.3)	188 (18.5)	162 (16.0)	0.13
Depression, Yes	146 (7.2)	74 (7.3)	72 (7.1)	<0.01

OHCA, out-of-hospital cardiac arrest

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Table 2. Characteristics of the study population according to the insomnia.

Variables	All	Insomnia (+)	Insomnia (-)	
	N (%)	N (%)	N (%)	p-value
All	2,028 (100.0)	543 (100.0)	1,485 (100.0)	
Case-control				0.17
OHCA case	1,014 (50.0)	272 (50.1)	742 (50.0)	
Community control	1,014 (50.0)	271 (49.9)	743 (50.0)	
Age				<0.01
18–29	38 (1.9)	7 (1.3)	31 (2.1)	
30–39	114 (5.6)	29 (5.3)	85 (5.7)	
40–49	276 (13.6)	80 (14.7)	196 (13.2)	
50–59	512 (25.2)	112 (20.6)	400 (26.9)	
60–69	544 (26.8)	159 (29.3)	385 (25.9)	
70–120	544 (26.8)	156 (28.7)	388 (26.1)	
Gender, female	554 (27.3)	183 (33.7)	371 (25.0)	<0.01
Metropolis, yes	1,028 (50.7)	297 (54.7)	731 (49.2)	0.86
Comorbidity				
Hypertension	823 (40.6)	249 (45.9)	574 (38.7)	<0.01
Diabetes	411 (20.3)	140 (25.8)	271 (18.2)	<0.01
Dyslipidemia	365 (18.0)	126 (23.2)	239 (16.1)	<0.01
Stroke	115 (5.7)	45 (8.3)	70 (4.7)	<0.01
Insurance, medical aid	210 (10.4)	66 (12.2)	144 (9.7)	0.47
Education level, high	646 (31.9)	162 (29.8)	484 (32.6)	<0.01
Obesity, yes	146 (7.2)	55 (10.1)	91 (6.1)	<0.01
Married, yes	1,544 (76.1)	415 (76.4)	1,129 (76.0)	<0.01
Work type				
Night work	362 (17.9)	91 (16.8)	271 (18.2)	<0.01
Shift work	178 (8.8)	57 (10.5)	121 (8.1)	<0.01
Physical activity				<0.01
Vigorous	365 (18.0)	78 (14.4)	287 (19.3)	
Moderate	549 (27.1)	141 (26.0)	408 (27.5)	
No	1,114 (54.9)	324 (59.7)	790 (53.2)	
Coffee, yes	697 (34.4)	157 (28.9)	540 (36.4)	<0.01
Smoking				<0.01
Current smoker	536 (26.4)	142 (26.2)	394 (26.5)	
Ex-smoker	597 (29.4)	156 (28.7)	441 (29.7)	
Non-smoker	895 (44.1)	245 (45.1)	650 (43.8)	
Alcohol drinking				<0.01
Heavy	617 (30.4)	170 (31.3)	447 (30.1)	
Moderate	661 (32.6)	162 (29.8)	499 (33.6)	
No	750 (37.0)	211 (38.9)	539 (36.3)	
Sleeping pill, yes	95 (4.7)	91 (16.8)	4 (0.3)	<0.01
Sleeping disorder				
Snoring	1,073 (52.9)	339 (62.4)	734 (49.4)	<0.01
Sleep apnea	350 (17.3)	119 (21.9)	231 (15.6)	0.13
Depression, yes	146 (7.2)	77 (14.2)	69 (4.6)	<0.01

OHCA, out-of-hospital cardiac arrest

Table 3. Characteristics of the study population according to the depression.

Variables	All	Depression (+)	Depression (-)	
	N (%)	N (%)	N (%)	p-value
All	1,748 (100.0)	146 (100.0)	1,602 (100.0)	
Case-control				<0.01
OHCA case	996 (57.0)	74 (50.7)	922 (57.6)	
Community control	752 (43.0)	72 (49.3)	680 (42.4)	
Age				1.00
18–29	34 (1.9)	1 (0.7)	33 (2.1)	
30–39	98 (5.6)	11 (7.5)	87 (5.4)	
40–49	242 (13.8)	35 (24.0)	207 (12.9)	
50–59	448 (25.6)	19 (13.0)	429 (26.8)	
60–69	472 (27.0)	37 (25.3)	435 (27.2)	
70-	454 (26.0)	43 (29.5)	411 (25.7)	
Gender, female	469 (26.8)	51 (34.9)	418 (26.1)	1.00
Metropolis, yes	890 (50.9)	101 (69.2)	789 (49.3)	0.86
Comorbidity				
Hypertension	727 (41.6)	57 (39.0)	670 (41.8)	<0.01
Diabetes	342 (19.6)	37 (25.3)	305 (19.0)	<0.01
Dyslipidemia	339 (19.4)	29 (19.9)	310 (19.4)	<0.01
Stroke	97 (5.5)	14 (9.6)	83 (5.2)	<0.01
Insurance, medical aid	170 (9.7)	30 (20.5)	140 (8.7)	0.47
Education level, high	591 (33.8)	34 (23.3)	557 (34.8)	<0.01
Obesity, yes	141 (8.1)	17 (11.6)	124 (7.7)	<0.01
Married, yes	1,407 (80.5)	106 (72.6)	1,301 (81.2)	<0.01
Work type				
Night work	346 (19.8)	20 (13.7)	326 (20.3)	<0.01
Shift work	171 (9.8)	11 (7.5)	160 (10.0)	<0.01
Physical activity				<0.01
Vigorous	347 (19.9)	20 (13.7)	327 (20.4)	
Moderate	510 (29.2)	31 (21.2)	479 (29.9)	
No	891 (51.0)	95 (65.1)	796 (49.7)	
Coffee, yes	669 (38.3)	41 (28.1)	628 (39.2)	<0.01
Smoking				<0.01
Current smoker	451 (25.8)	41 (28.1)	410 (25.6)	
Ex-smoker	539 (30.8)	42 (28.8)	497 (31.0)	
Non-smoker	758 (43.4)	63 (43.2)	695 (43.4)	
Alcohol drinking				<0.01
Heavy	545 (31.2)	42 (28.8)	503 (31.4)	
Moderate	597 (34.2)	47 (32.2)	550 (34.3)	
No	606 (34.7)	57 (39.0)	549 (34.3)	
Sleeping pill, yes	86 (4.9)	30 (20.5)	56 (3.5)	<0.01
Sleep disorder				
Insomnia	486 (27.8)	77 (52.7)	409 (25.5)	<0.01
Snoring	989 (56.6)	79 (54.1)	910 (56.8)	<0.01
Sleep apnea	328 (18.8)	32 (21.9)	296 (18.5)	0.13

OHCA, out-of-hospital cardiac arrest

Table 4. Multivariable conditional logistic regression analysis of insomnia and depression for out-of-hospital cardiac arrest.

OHCA incidence	OHCA cases/Community controls	Model 1			Model 2			Model 3			Model 3 (subgroup)		
	(n/n)	AOR	95% CI		AOR	95% CI		AOR	95% CI		AOR	95% CI	
Insomina (-)	742/743	1.00			1.00			1.00					
Insomnia (+)	272/271	0.92	0.74	1.13	1.00	0.80	1.25	0.95	0.64	1.40			
Depression (-)	900/937	1.00			1.00			1.00			1.00		
Depression (+)	114/77	1.49	1.08	2.06	1.23	0.87	1.73	0.86	0.67	1.10	2.30	1.26	4.20
Younger age (18–64)	602/599	1.00			1.00			1.00			1.00		
Older age (65–120)	412/415	1.07	0.75	1.53	1.18	0.81	1.70	1.40	0.93	2.12	1.19	0.57	2.48

OHCA, out-of-hospital cardiac arrest

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Discussion

The results of this multicenter case-control study demonstrated that insomnia and depression are not associated with an increased risk of OHCA. However, in the interaction analysis of insomnia and depression, insomnia with depression increased the risk of OHCA after adjusting for demographic characteristics and lifestyle behaviors, and this trend was significant only in the younger age group without insomnia medication. This research contributes to understanding the complex effects of insomnia and depression related to OHCA risk and will help develop strategies to reduce OHCA in the general population.

Sleep disturbance, including insomnia, has been reported as a risk factor of coronary heart disease and mortality in previous studies [25–27]. Insomnia has been shown to adversely influence physiological metabolism and endocrine function similar to that in premature aging, including altering the hypothalamic-pituitary-adrenal axis, reducing endogenous testosterone levels, and elevating biomarkers of chronic inflammation [9, 10, 28]. Contrary to the results of previous studies, insomnia alone did not increase OHCA risk in our study.

Previous studies suggested that depression and depressive symptoms are associated with an increased risk of coronary heart disease and OHCA [16, 29, 30]. This may be due to the fact that depression is associated with atherosclerosis, which is buildup of plaque in the arteries that can lead to cardiac events, alteration of the cardiac autonomic response, and a decrease in heart rate variability [31, 32]. Additionally, low red blood cell membrane levels of omega-3 polyunsaturated fatty acids, which is associated with an increased risk of sudden cardiac death, have been reported in patients with depressive disorders [33]. Omega-3 fatty acids have

Table 5. Interaction analysis for OHCA incidence of insomnia according to depression.

OHCA incidence	Insomnia (-)	Insomnia (+)				p for interaction
	AOR	AOR		95% CI		
Whole population (18–120)						0.03
Depression (-)	1.00	0.89	0.70		1.13	
Depression (+)	1.00	2.33	1.17		4.64	
Young population (18–64)						<0.01
Depression (-)	1.00	0.84	0.59		1.17	
Depression (+)	1.00	3.65	1.29		10.33	
Old population (65–120)						0.17
Depression (-)	1.00	0.87	0.60		1.27	
Depression (+)	1.00	1.73	0.64		4.68	

OHCA, out-of-hospital cardiac arrest

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anti-inflammatory and antiarrhythmic properties and can reduce the risk of developing atherosclerosis. However, our findings are in agreement with those of the prior studies, indicating that depression does not have an independent effect on OHCA risk. This suggest that while depression may be a risk factor for coronary heart disease and other cardiac events, it may not be a direct risk factor for OHCA.

Insomnia and depression, though separate disorders, have been shown to be highly interrelated in several previous studies. In a 2016 meta-analysis that analyzed the risk of depression in insomnia patients, the risk ratio of depression was 2.27 (95% CI: 1.89–2.71) among those with insomnia [34]. Additionally, symptoms of disturbed night-time sleep in individuals with depression have been suggested extensively in both clinical and epidemiological studies. In clinical studies, difficulty in initiating or maintaining sleep or both have been reported in about three-quarters of all depressive patients [35, 36]. In epidemiological studies examining insomnia and depression, sleep symptoms, including insomnia and hypersomnia, occurred in 50% to 60% in young adults [37]. In our study populations, 14.2% of insomnia patients had depression, while 52.7% of depression patients complained of insomnia. Regarding OHCA risk, insomnia and depression showed an interaction effect, and when insomnia was accompanied by depression, the OHCA risk was 2.33 times higher than when insomnia was not comorbid with depression, and this trend was maintained only in the young population under 65 years of age. A previous study on patients with coronary heart disease [38] reported that depression may be associated with mortality through negative health behaviors such as reduced physical activity.

Depression and insomnia are interconnected conditions that can negatively impact an individual's overall health and well-being. When both conditions are present, they may synergistic effect. For instance, depression is associated with neglecting health care needs, such as not seeking timely medical help, not adhering to prescribed treatments, and ignoring symptoms. This neglect can lead to worsening health outcomes and an increased risk of conditions such as OHCA. Insomnia, on the other hand, can contribute to the development or exacerbation of depression and further worsen an individual's health.

The relationship between insomnia and depression can create a vicious cycle, with each condition exacerbating the other. For example, chronic lack of restorative sleep due to insomnia may lead to the development or worsening of depressive symptoms. In turn, these depressive symptoms may disrupt sleep patterns and intensify insomnia. This continuous deterioration of both conditions not only heightens the risk of OHCA but also contributes to other adverse health outcomes. Moreover, insomnia and depression can intensify factors that increase OHCA risk, such as physiological changes, including increased inflammation, elevated stress hormones, and imbalances in the autonomic nervous system. The behavioral consequences of these conditions, like reduced physical activity, poor diet, and substance use, can further harm cardiovascular health.

A study was conducted in the UK on the incidence of insomnia in a wide range of patients of varying ages with depression. Overall, 83% of patients with depression had insomnia, which varied from 77% in the 16–24-year age group to 90% in the 55–64-year age group [39]. In our study, insomnia and depression showed a high trend in the elderly (those over 70 years of age); however, insomnia and depression did not increase the OHCA risk either alone or together in the elderly population.

In this study, neither insomnia nor depression alone increased the OHCA risk; however, insomnia with depression was associated with increased OHCA risk, and the effect of increased OHCA incidence was maintained only in the young population that did not consume insomnia medication. This may provide a theoretical basis for the need for early diagnosis and active treatment for insomnia patients with depression for lowering OHCA risk.

This study has several limitations. First, because histories of insomnia and depression were determined through self-report or through information obtained from the next of kin, rates of insomnia and depression may have been under- or over-estimated. Second, we did not investigate the treatment of depression in our registry questionnaire. There may be differences in the effect on OHCA risk depending on whether the disease is treated or not, which may have influenced the results of our study. Third, insomnia treatment other than medication could not be investigated in our registry. Finally, the study design was not a randomized controlled trial. There may have been a significant potential bias that was not controlled.

Conclusions

A multicenter case-control study found that neither insomnia nor depression alone increased the risk of OHCA. However, an interaction analysis of insomnia and depression revealed that two conditions together increased the risk of OHCA in the young population without insomnia medication.

The study suggests a need for further research and strategies to reduce OHCA risk in general population, particularly in young population with insomnia and depression. Early and active medical intervention for insomnia patients with depression may contribute to lowering the risk of OHCA.

Acknowledgments

Author Contributions

Conceptualization: Hyun Ho Ryu, Sung Wan Kim, Young Sun Ro.

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References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020; 141 (9):e139–e596. https://doi.org/10.1161/CIR.0000000000000757 PMID: 31992061

2. Bateman RM, Sharpe MD, Jagger JE, Ellis CG, Solé-Violán J, López-Rodríguez M, et al. 36th International Symposium on Intensive Care and Emergency Medicine: Brussels, Belgium. 15–18 March 2016. Critical care (London, England). 2016; 20(Suppl 2):94.

3. Lim ZJ, Ponnapa Reddy M, Afroz A, Billah B, Shekar K, Subramaniam A. Incidence and outcome of out-of-hospital cardiac arrests in the COVID-19 era: A systematic review and meta-analysis. Resuscitation. 2020; 157:248–58. https://doi.org/10.1016/j.resuscitation.2020.10.025 PMID: 33137418

4. Kim YS, Kim KH, Song KJ, Shin SD, Park JH. The number and level of first-contact emergency medical services crew and clinical outcomes in out-of-hospital cardiac arrest with dual dispatch response. Clin Exp Emerg Med. 2022; 9(4):314–22. https://doi.org/10.15441/ceem.22.205 PMID: 36216399

5. Lim HJ, Song KJ, Shin SD, Kim KH, Ro YS, Yoon H. Interactive effect of multi-tier response and advanced airway management on clinical outcomes after out-of-hospital cardiac arrest: a nationwide population-based observational study. Clin Exp Emerg Med. 2022; 9(3):187–97. https://doi.org/10.15441/ceem.21.169 PMID: 36146900

6. Spooner PM, Albert C, Benjamin EJ, Boineau R, Elston RC, George AL Jr., et al. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a national heart, lung, and blood institute workshop, part I. Circulation. 2001; 103(19):2361–4. https://doi.org/10.1161/01.cir.103.19.2361 PMID: 11352884

7. Spooner PM, Albert C, Benjamin EJ, Boineau R, Elston RC, George AL Jr., et al. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, Part II. Circulation. 2001; 103(20):2447–52. https://doi.org/10.1161/01.cir.103.20.2447 PMID: 11369684

8. Edinger JD, Bonnet MH, Bootzin RR, Doghramji K, Dorsey CM, Espie CA, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep. 2004; 27(8):1567–96. https://doi.org/10.1093/sleep/27.8.1567 PMID: 15683149

9. Motivala SJ. Sleep and inflammation: psychoneuroimmunology in the context of cardiovascular disease. Ann Behav Med. 2011; 42(2):141–52. https://doi.org/10.1007/s12160-011-9280-2 PMID: 21604067

10. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, et al. Sleep duration and biomarkers of inflammation. Sleep. 2009; 32(2):200–4. https://doi.org/10.1093/sleep/32.2.200 PMID: 19238807

11. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Prog Cardiovasc Dis. 2009; 51(4):294–302. https://doi.org/10.1016/j.pcad.2008.10.003 PMID: 19110131

12. Dew MA, Hoch CC, Buysse DJ, Monk TH, Begley AE, Houck PR, et al. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. Psychosom Med. 2003; 65(1):63–73. https://doi.org/10.1097/01.psy.0000039756.23250.7c PMID: 12554816

13. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry. 2002; 59(2):131–6. https://doi.org/10.1001/archpsyc.59.2.131 PMID: 11825133

14. Phillips B, Mannino DM. Does insomnia kill? Sleep. 2005; 28(8):965–71. https://doi.org/10.1093/sleep/28.8.965 PMID: 16218079

15. Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomér K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. Eur Heart J. 2000; 21(13):1072–80. https://doi.org/10.1053/euhj.1999.2012 PMID: 10843825

16. Empana JP, Jouven X, Lemaitre RN, Sotoodehnia N, Rea T, Raghunathan TE, et al. Clinical depression and risk of out-of-hospital cardiac arrest. Arch Intern Med. 2006; 166(2):195–200. https://doi.org/10.1001/archinte.166.2.195 PMID: 16432088

17. Prinz PN, Vitiello MV, Raskind MA, Thorpy MJ. Geriatrics: sleep disorders and aging. N Engl J Med. 1990; 323(8):520–6. https://doi.org/10.1056/NEJM199008233230805 PMID: 2198467

18. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007; 3(5 Suppl):S7–10. PMID: 17824495

19. Sin NL, Yaffe K, Whooley MA. Depressive symptoms, cardiovascular disease severity, and functional status in older adults with coronary heart disease: the heart and soul study. J Am Geriatr Soc. 2015; 63 (1):8–15. https://doi.org/10.1111/jgs.13188 PMID: 25597554

20. Strine TW, Chapman DP. Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. Sleep Med. 2005; 6(1):23–7. https://doi.org/10.1016/j.sleep.2004.06.003 PMID: 15680291

21. Ro YS, Shin SD, Song KJ, Kim JY, Lee EJ, Lee YJ, et al. Risk of Diabetes Mellitus on Incidence of Out-of-Hospital Cardiac Arrests: A Case-Control Study. PLoS One. 2016; 11(4):e0154245.

22. Yang JK, Kim YJ, Jeong J, Kim J, Park JH, Ro YS, et al. Low serum cholesterol level as a risk factor for out-of-hospital cardiac arrest: a case-control study. Clin Exp Emerg Med. 2021; 8(4):296–306. https://doi.org/10.15441/ceem.20.114 PMID: 35000357

23. Stahre M, Naimi T, Brewer R, Holt J. Measuring average alcohol consumption: the impact of including binge drinks in quantity-frequency calculations. Addiction. 2006; 101(12):1711–8. https://doi.org/10.1111/j.1360-0443.2006.01615.x PMID: 17156170

24. Aune D, Schlesinger S, Hamer M, Norat T, Riboli E. Physical activity and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies. BMC Cardiovasc Disord. 2020; 20(1):318. https://doi.org/10.1186/s12872-020-01531-z PMID: 32631241

25. Li SQ, Sun XW, Zhang L, Ding YJ, Li HP, Yan YR, et al. Impact of insomnia and obstructive sleep apnea on the risk of acute exacerbation of chronic obstructive pulmonary disease. Sleep Med Rev. 2021; 58:101444. https://doi.org/10.1016/j.smrv.2021.101444 PMID: 33601330

26. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. J Intern Med. 2002; 251(3):207–16. https://doi.org/10.1046/j.1365-2796.2002.00941.x PMID: 11886479

27. Li Y, Zhang X, Winkelman JW, Redline S, Hu FB, Stampfer M, et al. Association between insomnia symptoms and mortality: a prospective study of U.S. men. Circulation. 2014; 129(7):737–46. https://doi.org/10.1161/CIRCULATIONAHA.113.004500 PMID: 24226807

28. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999; 354(9188):1435–9. https://doi.org/10.1016/S0140-6736(99)01376-8 PMID: 10543671

29. Ahern DK, Gorkin L, Anderson JL, Tierney C, Hallstrom A, Ewart C, et al. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). Am J Cardiol. 1990; 66(1):59–62.

30. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation. 2002; 105(9):1049–53. https://doi.org/10.1161/hc0902.104707 PMID: 11877353

31. Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. Cleve Clin J Med. 2009; 76 Suppl 2(Suppl 2):S13–7. https://doi.org/10.3949/ccjm.76.s2.03 PMID: 19376975

32. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014; 129(12):1350–69. https://doi.org/10.1161/CIR.0000000000000019 PMID: 24566200

33. Tiemeier H, van Tuijl HR, Hofman A, Kiliaan AJ, Breteler MM. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. Am J Clin Nutr. 2003; 78(1):40–6. https://doi.org/10.1093/ajcn/78.1.40 PMID: 12816769

34. Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. BMC Psychiatry. 2016; 16(1):375. https://doi.org/10.1186/s12888-016-1075-3 PMID: 27816065

35. Hamilton M. Frequency of symptoms in melancholia (depressive illness). Br J Psychiatry. 1989; 154:201–6.

36. Yates WR, Mitchell J, John Rush A, Trivedi M, Wisniewski SR, Warden D, et al. Clinical features of depression in outpatients with and without co-occurring general medical conditions in STAR*D: confirmatory analysis. Prim Care Companion J Clin Psychiatry. 2007; 9(1):7–15. https://doi.org/10.4088/pcc.v09n0102 PMID: 17599162

37. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry. 1996; 39(6):411–8. https://doi.org/10.1016/0006-3223(95)00188-3 PMID: 8679786

38. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. Jama. 2008; 300(20):2379–88. https://doi.org/10.1001/jama.2008.711 PMID: 19033588

39. Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, et al. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep. 2006; 29(11):1391–7. https://doi.org/10.1093/sleep/29.11.1391 PMID: 17162985