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Heart rate variability as a potential biomarker for alcohol use disorders: A systematic review and meta-analysis

Ying-Chih Cheng[a,b,c], Yu-Chen Huang[c,d,e], Wei-Lieh Huang[f,g,h,i,*]

[a] Department of Psychiatry, Taoyuan Psychiatric Center Ministry of Health and Welfare, 71, Longshou Street, Taoyuan District, Taoyuan City 33058, Taiwan, ROC
[b] Department of Public Health and Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, No. 17, Xu-Zhou Road, Taipei 10055, Taiwan, ROC
[c] Research Center of Big Data and Meta-Analysis, Wan Fang Hospital, Taipei Medical University, No. 250 Wuxing St., Taipei 11031, Taiwan, ROC
[d] Department of Dermatology, Wan Fang Hospital, Taipei Medical University, 111, Hsing-Long Road Sec. 3, Wenshan District, Taipei City 11696, Taiwan, ROC
[e] Department of Dermatology, School of Medicine and College of Medicine, Taipei Medical University, No. 250 Wuxing St., Taipei 11031, Taiwan, ROC
[f] Department of Psychiatry, National Taiwan University Hospital, Yun-Lin Branch, No. 579, Sec. 2, Yunlin Rd., Douliu City, Yunlin County 64041, Taiwan, ROC
[g] Department of Psychiatry, National Taiwan University Hospital, No. 7, Zhongshan S. Rd., Zhongzheng Dist., Taipei City 10002, Taiwan, ROC
[h] Department of Psychiatry, College of Medicine, National Taiwan University, No. 1, Sec. 1, Ren'ai Rd., Zhongzheng Dist., Taipei City 10051, Taiwan, ROC
[i] Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, No. 7, Zhongshan S. Rd., Zhongzheng Dist., Taipei City 10002, Taiwan, ROC

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ABSTRACT

Background: Alcohol use disorders (AUDs) have been found to be associated with elevated cardiovascular risk. The autonomic nervous system is considered to play a role in this association. Heart rate variability (HRV) has been employed to measure parasympathetic activity in AUDs patients in some studies; however, the results are not consistent, and the adopted HRV indices vary across studies. A meta-analysis should be helpful for clarifying this topic.

Methods: We gathered studies about measuring HRV in AUDs patients and healthy participants from databases. HRV was analyzed in several ways: parasympathetic function in hierarchical order (main analysis), total variability, and specific parasympathetic indices. Specific parasympathetic indices were further separated into high-frequency power (HF) and root mean square of the successive differences (RMSSD). For comparing the above values in patients with AUDs and in healthy individuals, we adopted the random effects model to calculate the standardized mean difference.

Results: Of the 144 screened studies, 15 were included in the quantitative analysis. In the comparison of parasympathetic function in hierarchical order, HRV in AUDs patients was significantly lower than in healthy individuals (Hedges'g = −0.4301, 95% CI [−0.7601 to −0.1000], $p = 0.0106$, $I^2 = 83.8\%$). Regarding total variability and RMSSD, AUDs patients also had significantly lower values than healthy controls. However, the differences of specific parasympathetic indices and HF were not significantly different.

Conclusion: Our results support the view that AUDs patients have reduced parasympathetic activity. Total variability and RMSSD are suitable indices for presenting reduced HRV in patients with AUDs.

1. Introduction

Excessive alcohol use is an important worldwide health problem (Room et al., 2005). Aside from the general term "alcoholism," several different diagnostic constructs are used to describe this category of conditions: alcohol dependence syndrome, alcohol misuse in the International Statistical Classification of Diseases and Related Health Problems–10th Revision (ICD-10), alcohol dependence, alcohol abuse in the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV, the former diagnostic system), and alcohol use disorder in the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5, the current diagnostic system). Typically, only the diagnoses of one system are adopted in a single study (American Psychiatric Association, 2000, 2013; Connor et al., 2016; Robinson and Adinoff, 2016). Patients having these diagnoses, which we call "alcohol use disorders" (AUDs) for convenience in this article, suffer from negative impacts in biological, psychological, and social domains (Connor et al., 2016). In addition, long durations of alcohol exposure can cause

* Corresponding author at: Department of Psychiatry, National Taiwan University Hospital, Yun-Lin Branch, No. 579, Sec. 2, Yunlin Rd, Douliu City, Yunlin County 64041, Taiwan, ROC.
E-mail address: Y03046@ms1.ylh.gov.tw (W.-L. Huang).

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damage to various organs and systems. The central and peripheral nervous systems are all reported to be affected (Chopra and Tiwari, 2012; Johnson et al., 1986; Mukherjee, 2013). The activity of the autonomic nervous system is usually considered to be associated with the cardiovascular system (Thayer et al., 2010). Many studies have found patients with AUDs to have elevated cardiovascular and cerebrovascular risks (Emberson et al., 2005; Foerster et al., 2009; Mostofsky et al., 2016; Mukamal et al., 2005; Quintana et al., 2013). The role of autonomic regulation in these negative events is worthy of investigation.

The short-term effect of alcohol consumption is generally believed to be associated with autonomic activities. In the diagnostic criteria of alcohol withdrawal in the DSM-IV and DSM-5, autonomic hyperarousal is mentioned with presentations of diaphoresis, tachycardia, and hypertension (Jesse et al., 2017). Autonomic hyperarousal reflects sympathetic predominance, which could be related to elevated sympathetic or reduced vagal activities (Johnson et al., 1986). However, patients with AUDs are not always under withdrawal. For these patients, the autonomic presentations under intoxication, non-withdrawal states, and abstinence for a short duration cannot be directly understood in the manner of withdrawal symptoms. Heart rate variability (HRV) is a convenient, noninvasive tool for measuring autonomic (especially parasympathetic) functions. After the development of consensus in 1996, the 5-minute and 24-h HRV measurements have been standardized. There are several approaches for analyzing HRV such as time-domain, frequency-domain, and non-linear methods (Laborde et al., 2017; Shaffer and Ginsberg, 2017). Among various kinds of indices, a time-domain index root mean square of the successive differences (RMSSD), a frequency-domain index high-frequency power (HF), and respiratory sinus arrhythmia (RSA) with respiratory manipulation are considered the most specific parasympathetic measurements (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Kuo et al., 1999; Laborde et al., 2017; Quintana et al., 2016). The above constructs could be helpful for clarifying the autonomic features in patients with AUDs.

There have been dozens of observational and experimental studies to apply HRV measurement in patients with AUDs (Agelink et al., 1998; Bar et al., 2006, 2008; de Zambotti et al., 2014, 2015; Ganesha et al., 2013; Garland et al., 2012a, b; Herbsleb et al., 2013; Ingjaldsson et al., 2003; Irwin et al., 2006; Jochum et al., 2010; Karimullah et al., 2001). However, the adopted indices are heterogeneous between studies. Reduced parasympathetic activity was found in some studies, but the overall results are inconsistent (Agelink et al., 1998; Bar et al., 2006; Bar et al., 2008; de Zambotti et al., 2014, 2015; Ganesha et al., 2013; Herbsleb et al., 2013; Ingjaldsson et al., 2003; Irwin et al., 2006; Jochum et al., 2010; Karimullah et al., 2001). We consider that the indices in these studies can be separated into three categories: total variability (extended parasympathetic indices such as the time-domain index standard deviation of normal to normal RR intervals, SDNN, and the frequency-domain index total power, TP), specific parasympathetic indices (such as RMSSD and HF), and the ratio of low-frequency power to high-frequency power (LF/HF, some scholars suggested it to present sympathetic modulation or the balance of sympathetic and parasympathetic functions, but it is controversial; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Kuo et al., 1999). Separating the several types of data and performing meta-analyses will present the HRV features in patients with AUDs more clearly. There have been meta-analyses about HRV in patients with AUDs to support low vagal activity in these patients over the last 10 years, but until now, they did not include recent studies with large sample sizes, or they did not specifically investigate alcohol (Alvares et al., 2016; Quintana et al., 2013). Therefore, performing a new meta-analysis could provide more insight into the HRV presentations in patients with AUDs.

The present study is aimed at clarifying the HRV features in patients with AUDs via the integration of literature from academic databases. There are two major goals of this research. The first is to compare HRV in AUDs patients and healthy controls under the premise of including parasympathetic data as much as possible. The second is to perform subgroup analyses for clarifying whether extended (total variability) and specific (RMSSD, HF) parasympathetic indices have distinct results.

2. Methods and materials

2.1. Data sources and search strategy

This systematic review and meta-analysis was prepared according to the PRISMA statement guidelines (Moher et al., 2009a, 2009b). We conducted an electronic literature search of PubMed, the Cochrane Library, EMBASE, and PsychINFO from the earliest available date to September 2018. The literature search was conducted by three researchers and employed the search terms/key words without any limits: (“*alcohol use disorder*” OR “*alcohol dependence*” OR “*alcohol abuse*” OR “*alcoholics*” OR “*alcoholism*”) AND (“*heart rate variability*” OR “*HRV*” OR “*vagal nerve activity*” OR “*autonomic nervous system*” OR “*autonomic activity*”). All titles meeting the inclusion criteria were retrieved and reviewed in full text. Original studies reporting on HRV in patients with AUDs were eligible for review. HRV was defined as the primary outcome for meta-analyses, but other reported HRV measures were included as well. Additional eligible studies were sought by searching the reference lists from primary articles and relevant reviews to identify any further studies that were not found with the electronic search.

2.2. Inclusion and exclusion criteria

The eligibility criteria were: 1) the comparison of HRV in patients with a diagnosis of AUDs as defined by the Munich Alcoholism Test (MALT), the Diagnostic and Statistical Manual of Mental Disorders–Third Edition (DSM-III), the Diagnostic and Statistical Manual of Mental Disorders–Third Edition-Revised (DSM-III-R), DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition-Text Revision (DSM-IV-TR), or ICD-10 with healthy controls without AUDs; 2) studies that reported means and standard deviations of at least one HRV index or provided data to estimate these values (e.g., confidence intervals, interquartile range); and 3) published in English. Exclusion criteria were designs such as series of cases, case reports, and cross-sectional studies without comparison groups.

2.3. Data extraction and quality assessment

Three investigators independently extracted relevant information from the included studies and evaluated the methodological quality of eligible trials using the Newcastle-Ottawa Quality Assessment Scale (NOS; Stang, 2010). Information on studies was obtained regarding the total sample size, size of included groups, age, gender distribution, and the diagnostic criteria and measurement of HRV. Authors who reported HRV but did not provide sufficient quantitative data (e.g., only a graphical display) were contacted to request the necessary information to derive effect size estimates and confidence limits on the selected indices.

The NOS is a freely available eight-item scale with a version for assessing the quality of non-randomized studies in meta-analysis. This scale evaluates the domains of selection, comparability, and outcome or exposure. One star is allocated when a feature of quality is present up to a maximum of nine (the comparability domain can score up to two stars); studies awarded seven or more stars would be considered a high-quality study. All potentially relevant manuscripts were independently reviewed by two investigators, and areas of disagreement or uncertainty were adjudicated by a third investigator.

2.4. Outcome measures

We defined HRV as any measure reflecting parasympathetic function as the primary outcomes including RSA, HF (absolute, logarithmically transformed, and normalized values), RMSSD, TP, SDNN, nonlinear measures (e.g., approximate entropy), and standard deviation of RR intervals (SDRR). RSA, HF, and RMSSD are considered as more specific parasympathetic indices than other ones (Shaffer and Ginsberg, 2017). Secondary outcomes were defined as indices reflecting total variability (e.g., TP, SDNN) of HRV and indies reflecting on specific parasympathetic indices of HRV (e.g., HF, RMSSD).

2.5. Data synthesis and statistical analysis

We performed a pooled estimate of HRV in AUD patients compared to healthy controls. For indices reflecting three HRV categories, individual meta-analyses were performed. Where studies reported more than one index of HRV, hierarchical inclusion criteria were implemented to prevent conflation of effect-size estimates (Alvares et al., 2016). If the number of studies was sufficient, subgroup analysis of defined variables (LF/HF, HF, and RMSSD) were conducted. To estimate the true effect size across the different studies with variance in reported units, standardized mean differences (SMD; Hedges' g) with 95% confidence intervals were calculated. Hedges' g is related to Cohen's d and can be interpreted using the same conventions: small (0.2), medium (0.5), and large (0.8) (Cohen, 1988). An added benefit of Hedges' g is correction for biases found in small sample sizes. Both absolute and log-transformed values were included in the calculation of effect sizes. When only the standard error of the mean (SEM) was reported, standard deviation (SD) was calculated by multiplying the SEM by the square root of the sample size. In four studies, no data were retrieved on standard deviations; however, range and interquartile range were available. According to the Cochrane guidelines, standard deviations can be estimated from these (Higgins, 2011; Hozo et al., 2005).

Possible sources of heterogeneity or inconsistency among trials in the magnitude or direction of effects were investigated. Heterogeneity was performed using the I^2 test (Higgins and Thompson, 2002). A random effect model was employed in the presence of significant heterogeneity (Cochrane's Q P value < 0.1 and $I^2 > 50\%$). Publication bias was examined using a funnel plot, depicting the effect size against the standard error for asymmetry. Egger's regression test was also used to assess publication bias (Egger et al., 1997). Leave-one-study-out sensitivity analysis was performed by sequential exclusion of each trial to assess its influence on the net results.

To explore the potential effect of trial-level modifiers, we considered several covariates in meta-regression approaches conducted with one covariate at a time. Meta-regression allows the investigation of the effect of continuous and categorical characteristics. Three covariates were defined for the mean age, gender proportion, and study quality score. All meta-analytic computations were performed with the R software (R x64 3.5.1, The Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Baseline characteristics of included studies

Fig. 1 summarizes the review flowchart in accordance with the PRISMA statement (Moher et al., 2009a, 2009b). Of the 144 original studies screened, 28 studies met the inclusion criteria for qualitative synthesis (Agelink et al., 1998; Bar et al., 2006, 2008; Boschloo et al., 2011; Chen et al., 2015; Claisse et al., 2017; de Zambotti et al., 2014; DePetrillo et al., 1999; Eddie et al., 2013a; Ganesha et al., 2013; Herbsleb et al., 2013; Ingjaldsson et al., 2003; Irwin et al., 2006; Jochum et al., 2010; Karimullah et al., 2001; Malpas et al., 1991; Monforte et al., 1995; Murata et al., 1994; Penzlin et al., 2015; Rajan et al., 1998; Ray et al., 2017; Rechlin et al., 1996; Sucharita et al., 2009, 2012; Valladares et al., 2007; Weise et al., 1985, 1986; Yuksel et al., 2016). Of these, 10 studies that lacked detailed data (Chen et al., 2015; DePetrillo et al., 1999; Ingjaldsson et al., 2003; Irwin et al., 2006; Jochum et al., 2010; Karimullah et al., 2001; Monforte et al., 1995; Rechlin et al., 1996; Valladares et al., 2007; Weise et al., 1985) and whose corresponding authors could not be contacted were excluded from quantitative analysis. One study lacked a comparison group (Weise et al., 1986), and two studies examined whether AUDs comorbidity contributed an additive effect on HRV, so the control groups were not healthy subjects (Ray et al., 2017; Yuksel et al., 2016). A summary of included studies for qualitative synthesis and their results are presented in Table 1. The included studies had several designs; 22 were cross-sectional case-control studies, one was a clinical trial, and two were prospective cohorts. Of these, 17 studies concluded that AUDs patients had lower HRV values, while five studies showed contrary results. Another six articles revealed no difference between AUD patients and controls. A total of 15 articles (Agelink et al., 1998; Bar et al., 2006, 2008; Boschloo et al., 2011; Claisse et al., 2017; de Zambotti et al., 2014; Eddie et al., 2013a; Ganesha et al., 2013; Herbsleb et al., 2013; Malpas et al., 1991; Murata et al., 1994; Penzlin et al., 2015; Rajan et al., 1998; Sucharita et al., 2009, 2012) fulfilled the eligibility and provided detailed data of HRV between AUDs patients (n = 511) and age-matched controls (n = 873). The population size ranged from seven to 209. The mean age of AUDs patients was 36.33 years, ranging from 23.7 (Eddie et al., 2013a) to 50 (Murata et al., 1994), and the mean age of controls was 37.75 years, ranging from 20.5 (Eddie et al., 2013a) to 49 (Murata et al., 1994). The NOS scores of included studies for quantitative synthesis ranged from 5 to 9.

3.2. Meta-analyses of HRV values in patients with AUDs

The results of each meta-analysis are summarized in Table 2. Fifteen studies were extracted for synthesis of main effects. The meta-analysis of indices on parasympathetic function revealed a significant effect (Hedges'g = −0.4301, 95% CI [−0.7601 – −0.1000], $p = 0.0106$, $I^2 =$ 83.8%; see Fig. 2), indicating that individuals with AUDs have lower parasympathetic activity than healthy controls. The visual inspection of funnel plot for parasympathetic function revealed considerable asymmetry and a distribution of effect sizes concentrated to the left. Egger's regression test also indicated evidence of publication bias ($p =$ 0.002571; see Supplementary Fig. 1). Eleven studies were included in the meta-analysis of total variability of HRV, and the results also revealed a significant effect (Hedges'g = −0.6182, 95% CI [−0.9558 – −0.2805], $p = 0.0003$, $I^2 = 69.3\%$; see Fig. 3). A funnel plot and Egger's regression test indicated no publication bias ($p =$ 0.1815). Twelve studies reported on specific parasympathetic indices, and the results showed no significant differences (Hedges'g = −0.2386, 95% CI [−0.5456 – 0.0683], $p = 0.1276$, $I^2 = 79.5\%$; see Fig. 4). Visual inspection of the funnel plot revealed asymmetry. Egger's regression test indicated publication bias ($p =$ 0.02978).

3.3. Subgroup analysis

Subgroup analysis of the LF/HF ratio (Hedges'g = 0.1009, 95% CI [−0.3240 – 0.5259], $p = 0.6415$, $I^2 = 72.3\%$; see Supplementary Fig. 2) and of HF (Hedges'g = −0.2124, 95% CI [−0.5144 – 0.0897], $p =$ 0.1682, $I^2 = 65.2\%$; see Fig. 5) revealed no differences between patients with AUDs and controls. Subgroup analysis for RMSSD indicated that AUD patients had lower RMSSD values compared to controls (Hedges'g = −0.7026, 95% CI [−0.9816 – −0.4236], $p < 0.0001$, I^2 = 47.3%; see Fig. 6). After removing two articles with HRV reactivity (Herbsleb et al., 2013; Rajan et al., 1998), the results of resting-state HRV were similar to the original ones (see Supplementary Fig. 4).

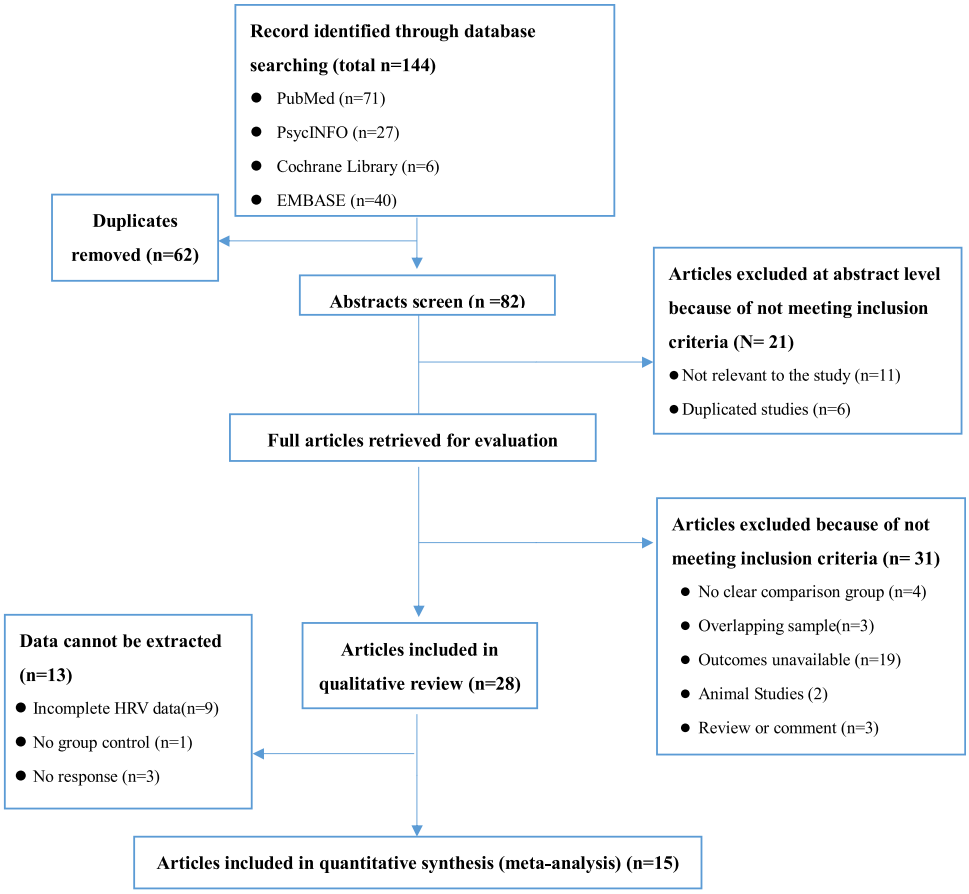

Fig. 1. PRISMA flow diagram of selection of studies included in the present systematic review and meta-analysis.

3.4. Sensitivity analysis

Of the six meta-analyses of HRV values, five were consistent with the full analysis after sequential exclusion of each trial, and no trial significantly affected our results. In sensitivity analyses of LF/HF, removal of one particular study (Bar et al., 2006) significantly altered the difference between patients with AUDs and healthy control individuals (see Supplementary Fig. 3). The effect size of LF/HF became statistically significant and positive in all cases, indicating an increased LF/HF in patients with AUDs compared to healthy controls.

3.5. Meta-regression

Analyses of study-level covariates showed no significant effect as a function of age, sex, or quality score (see Table 3). The results indicated that the moderator variables had no influence on our results ($p > 0.05$).

4. Discussion

There are three major findings of the present study. First, the results of the hierarchy approach reveal that patients with AUDs have lower vagal activity than healthy individuals. Second, separating total variability and specific parasympathetic indices, only the former revealed a significant difference between healthy individuals and AUDs patients. Third, considering RMSSD and HF, the former showed significant between-group differences. These findings are worthy of further discussion.

The most important finding of this research is that patients with AUDs have significantly lower parasympathetic activity than healthy controls. The effects of ethanol on the autonomic nervous system can be understood in both the short and long term. With regard to short-term effects, studies on healthy adults disclosed that alcohol consumption caused parasympathetic inhibition directly, which was dose-dependent (Sagawa et al., 2011). The short-term effect could be associated with phasic activity of parasympathetic system; working as a central nervous system depressant, alcohol inhibits the nucleus ambiguus, causing repression of the synchronizing ability between respiration and vagal activity, and finally resulting in dose-dependent inhibition of parasympathetic activity (Sagawa et al., 2011; Yasuma and Hayano, 2004). As for the long-term effect, ethanol per se has neurotoxicity and has been proved to impair both central and peripheral nervous systems (Chopra and Tiwari, 2012; Mukherjee, 2013). Therefore, damage to the autonomic nervous system by ethanol is not surprising. The impacts of chronic, excessive ethanol exposure on the autonomic nervous system can result from the autonomic damage per se and via the central nervous system. The former might explain impotence, problems of gastrointestinal motility (under damage to the parasympathetic system), orthostatic hypotension, and abnormality of sweating function (under damage to the sympathetic system), all of which are common in patients with AUDs (Johnson et al., 1986). In the latter condition, an example is injury to the hypothalamus caused by ethanol toxicity or comorbidities (such as thiamine deficiency), which affect efferent autonomic regulation (Johnson et al., 1986). These are possible explanations of the reduced vagal activity in AUDs patients revealed in our analysis.

The result of the above main analysis revealed publication bias. Several studies with low NOS could contribute to heterogeneity (Boschloo et al., 2011; Eddie et al., 2013b; Malpas et al., 1991; Penzlin et al., 2015). Therefore, we performed an extra sensitivity analysis for clarifying the influence of these studies. After deleting four studies with NOS less than 7 (Boschloo et al., 2011; Eddie et al., 2013b; Malpas

Table 1
Characteristics of the included studies.

Author Year	Study design	HRV analysis	Comparison	Diagnosis Criteria	Age(SD or Range)	Male	Major finding	Quality (NOS)
Weise et al., 1985	Case control	MMA, HR	31 Alcoholic 106 Healthy	MALT	35.9(17–55) 31.7(17–67)	22 58	Lower MMA in alcoholic	7
Weise et al., 1986	Cohort	MMA, HR	11 Alcoholic 7 Healthy	MALT	40.5 (4.5) 25.6(3.2)	9 5	Increased HRV in alcoholic with prolonged abstinence	7
Malpas et al., 1991	Case control	SDSD, Valsalva ratio	7 AD 11 Healthy	NR	54 (37–72) NR	23 11	Lower SDSD in AD	5
Murata et al., 1994	Case control	CVRR, HF, LF	23 AD 23 Healthy	DSM-III-R	50(30–64) 49(30–63)	23 23	Lower CVRR, HF, LF in AD	7
Monforte et al., 1995	Case control	Valsalva ratio	107 Alcoholic 61 Healthy	NR	43(11) 41(14)	89 51	Lower Valsalva ratio in alcoholic	5
Rechlin et al., 1996	Case control	CVr, MF, HF, LF	60 AD 60 Healthy	DSM-III-R	40.1(19–64) 40.5(19–61)	43 43	Lower HF and lower CVr in AD	7
Agelink et al., 1998	Case control	CVr, RMSSD, HF, LF, MF	35 AD 80 Healthy	DSM-III-R	42.9(10) 41.8(14.7)	20 47	Lower RMSSD and CVr in AD	7
Rajan et al., 1998	Case control	CVr, HF, LF	20 ADS 23 Social drinker	ICD-10	33.75(6.3) 33.17(6.4)	20 23	Higher HF in AD under neutral cue	7
DePetrillo et al., 1999	Case control	IBI, Hurst exponent	13 AD 48 Healthy	DSM-III	40(3.8)* 40.3(2.7)*	7 15	Higher Hurst exponent in AD	8
Karimullah et al., 2001	Case control	TP, LF, HF, IBI, Hurst exponent	20 AD 48 Healthy	DSM-III-R	41.4(1)* 40(3.8)*	16 15	Higher Hurst exponent in AD	7
Ingjaldsson et al., 2003	Case control	NR	49 Alcoholic 45 Healthy	NR	45(NR) 42(NR)	37 NR	Lower HRV in alcoholic	5
Bar et al., 2006	Case control	RMSSD, HF, LF/HF	15 abstained AD 20 Healthy	DSM-IV	43.4(11.1) 47.5(5.16)	15 20	Lower RMSSD in AD	7
Irwin et al., 2006	Cohort	HF, LF	14 AD 14 Healthy	DSM-IV	39.1(6.4) 37.5(9.8)	14 14	Lower HF in AD	8
Valladares et al., 2007	Case control	HF, LF	NR abstained AD NR Healthy	NR	25(NR) 26(NR)	NR NR	Lower HF and higher LF/HF in AD	4
Bar et al., 2008	Case control	ApEn, phvar, plvar	20 AD 20 Healthy	DSM-IV MALT	42(33–58) 42(27–56)	20 20	No difference in ApEN	7
Sucharita et al., 2009	Case control	SDRR, CVRR%	17 Alcohol abuse 17 Healthy	AUDIT	40.4(8.4) 40.7(8.5)	16 17	Lower SDRR and CVRR in alcohol abuse	7
Jochum et al., 2010	Case control	LF/HF, LF	20 AWS at admission 20 Healthy	DSM-IV	37.9(6.1) 41.1(9.2)	20 20	Higher LF/HF and LF in AWS at admission	8
Boschloo et al., 2011	Case control	RSA	208 Current AD 498 No Alcohol use	DSM-IV	39.1(12.2) 42.7(12.8)	99 115	No significant difference	6
Sucharita et al., 2012	Case control	TP, HF, LF	27 ADS 27 Healthy	ICD-10	35.6(7.3) 35.4(7.9)	27 27	No difference in supine position	7
Eddie et al. 2013	Case control	SDNN, HF, LF	28 AUD 43 Healthy	NR	23.7(3.5) 20.5(1.6)	NR NR	Lower SDNN, HF, LF in AUD	5
Ganesha et al., 2013	Case control	SDNN, RMSSD, TP, HF, LF, LF/HF	20 ADS 18 Healthy	ICD-10	38.8(NR) 39.7(NR)	20 20	Lower SDNN, RMSSD, TP, LF, HF in ADS	7
Herbsleb et al., 2013	Case control	Compression entropy, RMSSD	22 AD 22 Healthy	DSM-IV	31(7) 34(8)	20 19	Lower compression entropy, RMSSD in AD	7
de Zambotti et al. 2014	Case control	SDNN, RMSSD, TP, HF, LF/HF	14 recently abstaining AD 16 Healthy	DSM-IV	42(9) 45.2(9.1)	7 8	Lower SDNN and lower HF in AD	7
Chen et al., 2015	Case control	Total HRV, LF, HF	24 AD 120 Healthy	DSM-IV	46.23(9.9) 41.29(12.1)	21 105	Lower total HRV in AD	8
Penzlin et al., 2015	RCT	TP, HF, LF	24 AD 24 Healthy	DSM-IV	40(7) 44(8)	17 17	No difference	5
Yuksel et al., 2016	Case control	SDNN, RMSSD, TP, HF, LF	20 AD + Nicotine dependence 22 Nicotine dependence	DSM-IV-TR	41.2(8) 27.88(4.89)	20 22	Lower TP and HF in AD + Nicotine dependence	4
Claisse et al., 2017	Case control	HF	31 AUD with short-term abstinence 31 Healthy	DSM-5	44.38(7.73) 41.61(9.14)	22 22	No difference	7
Ray et al., 2017	Case control	SDNN, RMSSD, HF	29 AUD + PTSD 41 PTSD	DSM-IV	35.2(5.4) 32.1(6.7)	29 41	No additive effects of PTSD and AUD on HRV	6

AD, alcohol dependence; ADS, alcohol dependence syndrome; ApEn, approximate entropy; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; AWS, alcohol withdrawal symptoms; CVRR, Coefficient of variation -RR intervals; DSM, The Diagnostic and Statistical Manual of Mental Disorders; HF, high-frequency power; HR, heart rate; IBI, interbeat interval ; ICD-10, The International Statistical Classification of Diseases and Related Health Problems 10th Revision; LF, low-frequency power; LF/HF, ratio of low-frequency power to high-frequency power; MALT, Munich Alcoholism Test; MF, mid frequency power; MMA, momentary arrhythmia; NOS, Newcastle-Ottawa Quality Assessment Scale; NR, not reported; RCT, randomized controlled trial; SDRR, standard deviation of RR intervals; SDNN, standard deviation of all normal to normal RR intervals; TP, total power; RSA, respiratory sinus arrhythmia; RMSSD, root mean square of the successive differences.

* Using standard estimate (SE) rather than standard deviations (SD).

et al., 1991; Penzlin et al., 2015), HRV in AUDs patients and in healthy controls were still significantly different (Hedges'g = −0.4642, 95% CI [−0.8257 – −0.1026], p = 0.0119, I^2 = 75.1%), and the result of Egger's test indicated no publication bias (p = 0.1163). Therefore, we believe the significant difference in the main analysis to be robust.

Our analysis reveals total variability to show more difference

Table 2
Meta-analysis result of HRV in patients with alcohol use disorders.

	Study No	Patients /Control	Effect sizes(95%CI)	Effect size p value	Heterogeneity I^2 (%)
Groups by HRV parameters (parasympathetic function, in hierarchical order)	15	511/873	−0.4301 (−0.7601 to −0.1000)	0.0106	83.8%
Groups by total variances of HRV parameters	11	238/278	−0.6182 (−0.9558 to −0.2805)	0.0003	69.3%
Groups by specific parasympathetic indices of HRV parameters	12	467/825	−0.2386 (−0.5456–0.0683)	0.1276	79.5%
Groups by LF/HF	7	154/204	0.1009 (−0.3240–0.5259)	0.6415	72.3%
Groups by HF	10	237/305	−0.2124 (–0.5144–0.0897)	0.1682	65.2%
Groups by RMSSD	4	92/140	−0.7026 (−0.9816 to −0.4236)	< 0.0001	47.3%

HRV, heart rate variability; LF/HF, ratio of low-frequency power to high-frequency power; HF, high-frequency power; RMSSD, root mean square of the successive differences.

between AUDs patients and controls than specific parasympathetic indices. Therefore, it seems adequate to use total variability for measuring vagal activity in patients with AUDs. A possible explanation is that some measurements beyond the specific parasympathetic indices (such as low-frequency power, LF) also correspond to different parasympathetic activity between patients with AUDs and healthy ones. It causes TP and SDNN to reflect more intact vagal activities. LF is generally considered to represent combining sympathetic, parasympathetic, and baroreflex functions; some studies suggest that LF also tends to reflect vagal modulation (Reyes del Paso et al., 2013; Shaffer and Ginsberg, 2017). It is reported that sympathetic activity rarely presents in frequency-band higher than 0.1 Hz; however, the lower limit of parasympathetic activity is around 0.05 Hz (Shaffer and Ginsberg, 2017; Shaffer et al., 2014). It indicates that LF and HF might reflect mainly vagal activity in some situations (such as low respiratory rate). In the 5-minute HRV, TP is composed of HF, LF, and very low-frequency power (VLF). Therefore, TP possibly reflects more parasympathetic activity than HF because it also contains LF. VLF should not be associated with parasympathetic modulation. This hypothesis awaits further examination.

Based on the above finding about specific parasympathetic indices, we separated RMSSD and HF for performing subgroup analysis. We found significant between-group differences in RMSSD but not in HF. The negative result of HF is somewhat surprising because HF, RMSSD, and RSA are highly correlated (Allen et al., 2007; Shaffer and Ginsberg, 2017). The negative finding of HF can be explained in two ways. The first is as described above; the different parasympathetic activity between AUDs patients and healthy individuals is within the range of both HF and LF bands. Therefore, HF only reflects partial vagal activity. The second explanation is that as the HF formats (including absolute, logarithmically transformed, and normalized values) are heterogeneous between studies (and hence more heterogeneous than RMSSD), data distortion might appear during the integrating process (Bar et al., 2006; de Zambotti et al., 2014; Ganesha et al., 2013; Irwin et al., 2006; Rajan et al., 1998). Compared with HF, RMSSD can present more intergroup differences. RMSSD has been found to be affected by respiratory rate in a minor degree (Hill and Siebenbrock, 2009). However, the number of included studies involving RMSSD is low, and more of this kind of studies are warranted.

LF/HF is slightly higher in patients with AUDs, but the intergroup difference is not significant. The result is not surprising, because the clinical meaning of LF/HF is controversial (the common viewpoint is to represent the balance between sympathetic and vagal activities); LF/HF was not adopted as a main observing index in many HRV studies (Shaffer and Ginsberg, 2017; Shaffer et al., 2014). Some scholars considered the fluctuation of LF/HF to be mainly resulting from the change of LF, which is not a pure sympathetic index (Shaffer et al., 2014). As we discussed above, if the LF band reflects more vagal activity in patients with AUDs, it follows that LF/HF cannot represent the true sympathovagal balance. The heterogeneity of the included studies is another explanation. According to the result of sensitivity analysis, after excluding the Bar and coworkers' 2006 research (Bar et al., 2006), which focused on AUDs patients with short-term abstinence, LF/HF became significantly higher in patients with AUDs than in controls. It is possible that the effect of LF/HF elevation is relatively short, which cannot persist until ceasing alcohol drinking. Therefore, under the status of short-term abstinence, the LF/HF reduces to normal range, whereas the reduced parasympathetic activity can still be observed. The hypothesis awaits further exploration.

Several limitations of the study should be mentioned. First, the definition of "problematic alcohol consumption" is different across studies. The literature included in our analysis spans 30 years, and the

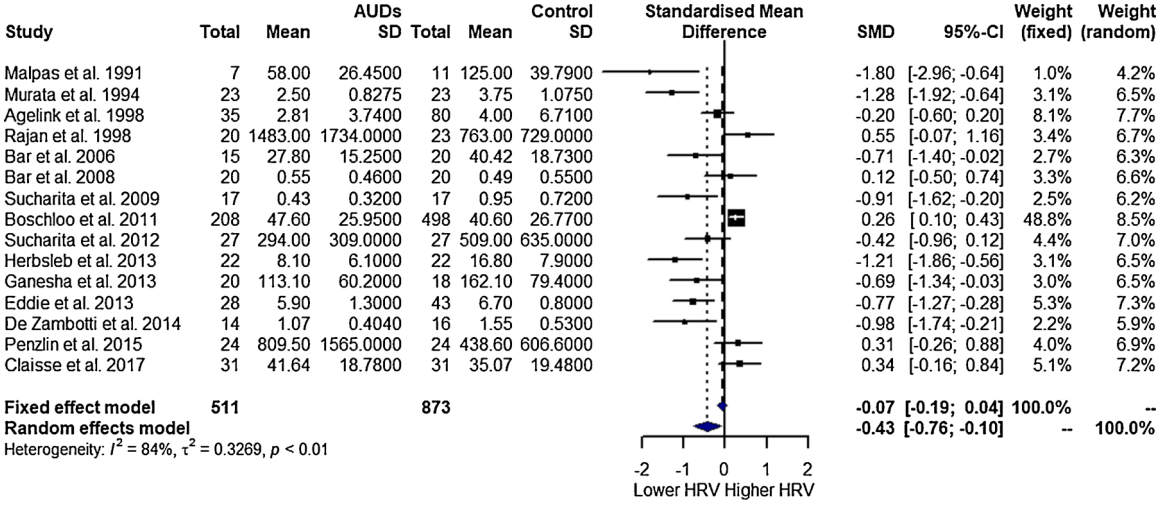

Fig. 2. Forest plot of Meta-Analysis on HRV (parasympathetic function, in hierarchical order). HRV, heart rate variability.

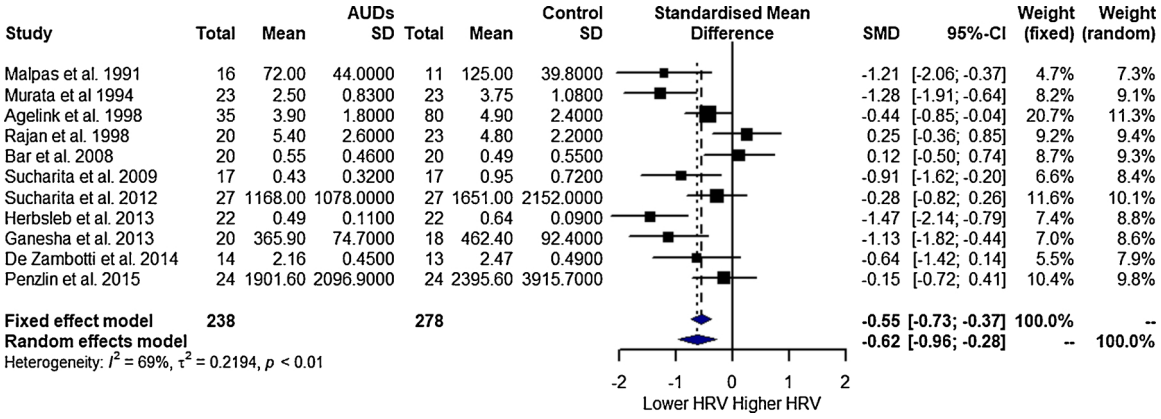

Fig. 3. Forest plot of Meta-Analysis on total variability of HRV parameters. HRV, heart rate variability.

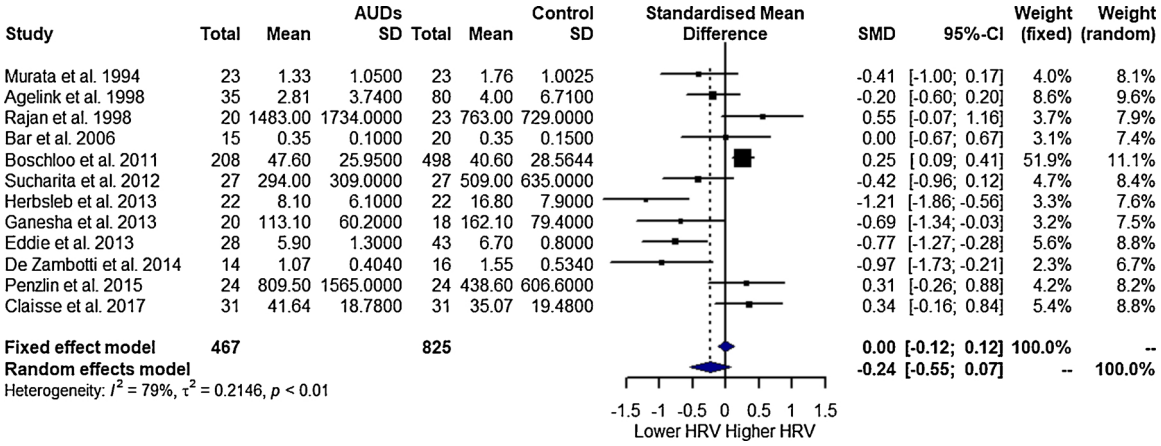

Fig. 4. Forest plot of Meta-Analysis on parasympathetic indices of HRV. HRV, heart rate variability.

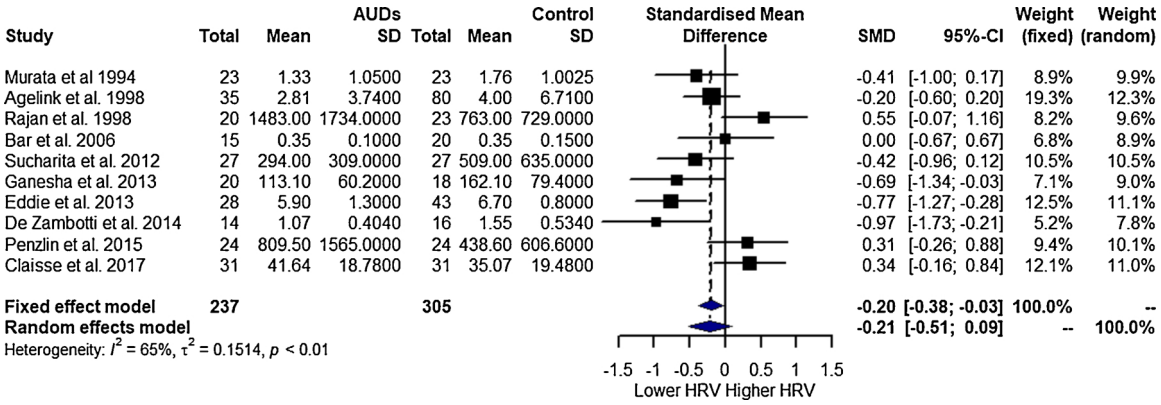

Fig. 5. Forest plot of Meta-Analysis on HF. HF, high-frequency power.

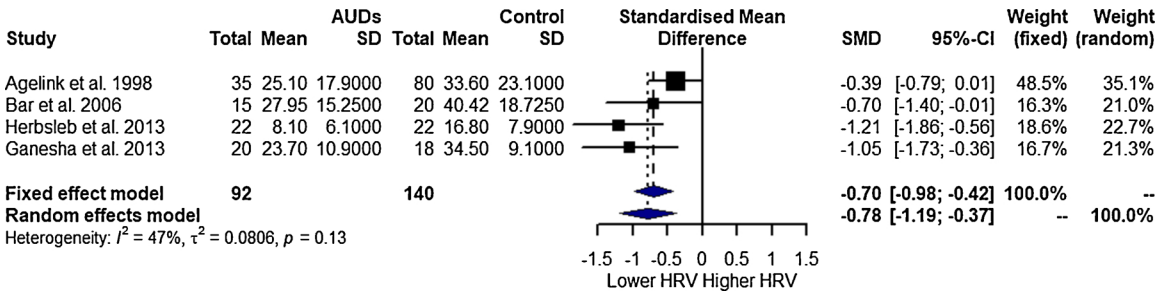

Fig. 6. Forest plot of Meta-Analysis on RMSSD. RMSSD, root mean square of the successive differences.

Table 3
Meta-regression of pre-defined variables of interest.

Covariate	Number of studies	Meta-regression		Proportion of variance explained
		ß(95% CI)	*p* value	
Age	15	−0.0272 (−0.0857–0.0312)	0.3615	0.00%
Sex	14	−0.0027(−0.0142–0.0088)	0.6479	0.00%
Risk of bias	15	0.0098(−0.4226–0.4421)	0.9646	0.00%

gold standards for making this kind of diagnosis are changing. For example, in the DSM-IV era, the most commonly used concept is alcohol dependence, and alcohol use disorder became much more frequent in the DSM-5 era. The two constructs are overlapping but not identical; alcohol use disorder integrates the concepts of alcohol dependence, alcohol abuse, and craving (Connor et al., 2016). Second, the indices are not identical among studies. Even for the frequency-domain index HF, different ways of presentation (such as absolute value, logarithmically transformed value, and normalized value) were found among studies. If some data do not have Gaussian distributions, the results of integration might be influenced. However, to our knowledge, it is a common pitfall in most meta-analyses involving HRV. Only limited studies adopting RSA or nonlinear measures (Bar et al., 2008; Boschloo et al., 2011) were incorporated into our meta-analysis; therefore, the interpretation of these concepts should be cautious. Third, the situations during measurement in included studies varied somewhat. Though alcohol users were recruited in all studies, several studies measured HRV during withdrawal status (Jochum et al., 2010), several were focused on ones with short-term abstinence (Bar et al., 2006), and several studies included patients under psychological observation (Rajan et al., 1998). The heterogeneity might have an influence on the results. We considered performing subgroup analyses for managing the heterogeneity, but because of the distinct indices in these studies, this approach seems unable to provide more meaningful understanding. Besides, excluding HRV reactivity data does not change the significance of the results. Fourth, the influence of other physical/psychological comorbidities and medications cannot be excluded. HRV is sensitive and can be affected by various types of factors such as sex, age, depression, anxiety, diabetes mellitus, anti-arrhythmic agents, and tricyclic antidepressants (Alvares et al., 2016; Kemp et al., 2010; Laborde et al., 2017). Although some above confounders have been excluded in several included studies, considering the physical and psychological conditions of AUDs patients, the possibility of coexistence of these factors is not low. We used meta-regression to examine the sex- and age-related effects of HRV, and the influence seemed non-significant. However, confounding from other factors still cannot be ruled out. Finally, many of the included studies were relatively small and included patients with different subtypes of AUDs; thus, they investigated quite heterogeneous populations, which together could increase the risk of spurious findings (Egger et al., 1998). In addition, many of the studies did not provide information on clinical characteristics such as severity of alcohol use, illness duration, medication use, methods of recording HRV, and the use of different software tools for analysis of HRV, which precluded meta-regression analyses on these variables. Given the unknown relationship between these factors and HRV, they could be important sources of the observed heterogeneity across studies. Furthermore, the present analysis did not address the influence of other variables that have been identified by previous meta-analyses such as ethnicity (which has been shown to account for individual differences in HRV).

Among the confounding factors, cigarette smoking especially should be discussed because a high proportion of AUDs patients have smoking habits. The impact of tobacco use on HRV has also been reported (Laborde et al., 2017). Among the articles we reviewed, tobacco use was mentioned in 10 of them (Bar et al., 2006; Boschloo et al., 2011; Chen et al., 2015; de Zambotti et al., 2014; Herbsleb et al., 2013; Irwin et al., 2006; Jochum et al., 2010; Penzlin et al., 2015; Ray et al., 2017; Yuksel et al., 2016), and our meta-analysis included five of the above articles (Bar et al., 2006; Boschloo et al., 2011; de Zambotti et al., 2014; Herbsleb et al., 2013; Penzlin et al., 2015). Because of the limitations of the data, we are unable to use meta-regression or the subgroup analysis to analyze the influence of comorbid smoking with AUDs on HRV. However, in one article (Yuksel et al., 2016), the effect of comorbid smoking and AUDs on HRV was discussed. In this article, the subjects were separated into three groups: smoking with alcohol, smoking, and control. The smoking with alcohol group revealed the lowest HRV values. Therefore, it is possible that comorbid smoking could aggravate the effect of HRV reduction in AUDs patients.

5. Conclusion

In summary, our results support reduced vagal activity in patients with AUDs. Moreover, the differences between AUDs patients and healthy individuals were more significant when choosing total variability and RMSSD as indices. In the clinical domain, the findings imply that total variability and RMSSD could be helpful for distinguishing AUDs patients from healthy individuals. Total variability and RMSSD can be viewed as candidates for diagnostic biomarkers. From a research perspective, the results could be meaningful for exploring the effects of ethanol on the autonomic nervous and cardiovascular systems and the risks it poses. We expect our findings about total variability and RMSSD to be examined by more well-designed studies in the future. Also, it is difficult to explore the sympathetic nervous system comprehensively by measuring only HRV. Therefore, specific sympathetic indices (such as galvanic skin response and pre-ejection period) should also be considered in future studies (Beauchaine et al., 2013; Robinson and Demaree, 2009).

Contributors

Y.C. Cheng and W.L. Huang reviewed the literature and designed this study. Y.C. Cheng and Y.C. Huang analyzed and interpreted the data. Y.C Cheng and W.L. Huang drafted the manuscript.

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Nothing declared.

Declaration of Competing Interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.05.030.

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