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Worldwide prevalence of early repolarization pattern in general population and physically active individuals

A meta-analysis

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Abstract

Background: The early repolarization pattern (ERP) has recently been associated with cardiac events such as ventricular arrhythmias and sudden cardiac death. However, estimates of the prevalence of ERP vary widely, especially between the general population and physically active individuals. We performed this systematic review and meta-analysis to quantitatively evaluate the worldwide prevalence of ERP in the general population and physically active individuals.

Methods: We thoroughly searched the PubMed, EMBASE, Web of science, the Cochrane Library, and Scopus databases for relevant studies published until December 20, 2020. Studies in which prevalence was presented or could be estimated from eligible data were included. The pooled prevalence was analyzed using a random-effect model.

Results: Finally, we included 29 studies (182,135 subjects) in the general population and 14 studies (8087 subjects) in the physically active individuals. The worldwide pooled prevalence of ERP in the general population was 11.6% (95% confidence interval [CI]: 10.0%–13.3%). The incidence of ERP was 17.0% and 6.2% in men and women, respectively. The prevalence was 20.9% in blacks, 13.4% in Asians, and 10.1% in Caucasians. Additionally, the prevalence of ERP in physically active individuals was 33.9% (95% CI: 25.3%–42.6%).

Conclusion: A significant difference in the worldwide prevalence of ERP is revealed in this study. The ERP is highly prevalent in men, blacks, and physically active individuals.

Abbreviations: CI = confidence interval, ECG = electrocardiogram, ERP = early repolarization pattern, NOS = Newcastle–Ottawa quality assessment scale, PRISMA = preferred reporting items for systematic reviews and meta-analyses statement.

Keywords: early repolarization pattern, meta-analysis, prevalence

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1. Introduction

Early repolarization pattern (ERP), which has been first described in 1936 by Shipley and Hallaran,[1] is generally defined as J-point elevation with QRS notching or slurring in the terminal part of the QRS complex detected by the standard 12-lead electrocardiogram (ECG).[2,3] ERP was once considered as a normal variant of ECG and even a sign of good health.[2] However, in recent years there is a growing recognition that early repolarization is associated with adverse outcomes. It has been reported that ERP increases the risk of idiopathic ventricular fibrillation, lone atrial fibrillation, and other arrhythmia events.[4–10] Furthermore, ERP has recently been reported to be associated with significant increased risk for sudden cardiac arrest and future arrhythmic death, which raises clinical and medicolegal concerns among cardiologists.[11–13]

Previous studies have indicated that ERP shows sex- and ethnicity-related penetrance. It is well known that its prevalence seems to be higher in men and blacks.[1,14–17] Because of different region and population, the prevalence of ERP is highly variable due to heterogeneity of each study.[18–20] In addition, previous studies have also investigated the difference in incidence of ERP between physically active individuals and the general population.[21,22] Several studies have reported that ERP is more commonly seen in physically active individuals.[1,21–23]

Up to now, although the prevalence of ERP has been reported in several regions and countries, no systematic evaluation has

been done to report the specific worldwide prevalence of ERP. Therefore, we conducted this systematic review and meta-analysis to identify the worldwide prevalence of ERP in the general population and in physically active individuals.

2. Methods

2.1. Search strategy and selection criteria

Under the guidance of the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA), we independently examined related English articles published up to December 20, 2020 by searching the PubMed, EMBASE, Web of science, the Cochrane Library, and Scopus databases. The search strategies were constructed by combining key words and related database-specific subject terms to search appropriate articles. The eligible words including "early repolarization pattern," "ERP," "early repolarization," "J-wave," "Osborn wave," "prevalence," and "incidence" were used. In addition, we hand-searched all the reference lists of the included articles to identify all relevant studies.

The titles and abstracts of the retrieved articles were independently examined by 3 review authors (H-YJ, NH, and RL), and any articles that were obviously irrelevant were excluded. Then the full texts of the remaining studies were reviewed and screened using the eligibility criteria. The inclusion criteria and exclusion criteria of study were as follows: studies were used that contained a clear definition of ERP proposed by Macfarlane et al[3] and Haissaguerre et al.[5] Prevalence of ERP was reported using either clinical ECG data or a follow-up experiment in the crowd or in the certain studying cohort. If not, sufficient data must be available to calculate the prevalence exactly. Studies that discussed prospective relationships between ERP prevalence and age, sex, occupation, ethnicity, or other clinical characteristics were included. The characteristics of the sample must be demonstrated thoroughly and exactly, articles that contained insufficient statistics would be excluded. Apparently healthy individuals and asymptomatic outpatients were employed and individuals who had any evidence of structural heart diseases were excluded from this meta-analysis. Physically active individuals include athletes and military officers.

2.2. Data extraction and quality assessment

From the articles taken into inclusion, useful information was independently extracted by 3 investigators (H-YJ, NH, and RL). Any disagreements were resolved by discussion with other investigators. The extracted data were as follows: first author's name, year, and country of publication, sample size, study design, definition of ERP, study population, average age, percentage of men, ethnicity, the ERP incidence, the percentage of men and women in ERP subjects.

Study quality was judged based on the Newcastle–Ottawa quality assessment scale (NOS) by 2 independent reviewers (H-YJ and X-QQ) using the following factors: study design, inclusion criteria, sample capacity, the sex ratio, and clear diagnostic criteria.

2.3. Ethics

In this study, ethical approval was not necessary because the included data were based on previous published articles, and no original clinical data were collected or utilized.

2.4. Statistical analysis

A random-effect model developed by DerSimonian and Laird was applied to estimate pooled prevalence and 95% confidence interval (CI) because we found that significant heterogeneity was present between studies after using the heterogeneity test. The heterogeneity among studies was quantified using the Cochran' Q test, and the magnitude of heterogeneity was assessed using the I^2 statistic. An $I^2 > 75\%$ indicated high statistical heterogeneity.[11] Sensitivity analysis was performed by omitting 1 specific study at a time to examine whether the pooled prevalence could have been influenced by any included studies. Finally, the subgroup analysis was performed based on sexes (men vs women), ethnicities, and geographical regions.

Forest plots consisting of the point estimations of prevalence and their 95% CI for all included studies were constructed and statistical significance was defined as a P value $<.05$. We performed all analyses by using Stata version 16.0 (StataCorp, College Station, TX).

3. Results

3.1. Study selection

Results on literature search and literature selection for the calculation of prevalence were presented in detail (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G173, Supplemental Content, which illustrates the information flow of the search and selection of studies). We identified 723 papers with the initial search strategy. Additionally, 15 articles were retrieved from reference lists of included studies. Of the 738 unique articles, 534 studies were discarded after reading the title and abstract. Of the 204 studies selected for full-text review, 151 studies were excluded due to inadequate information and 10 studies were discarded for unclear ERP definition. Thus, the remaining 43 studies (29 studies that reported prevalence in general population and 14 studies that reported prevalence in physically active individuals) with 190,222 subjects were included in this meta-analysis.

3.2. Study characteristics

The characteristics of the 29 included studies involving a total general population of 182,135 subjects are shown in Table 1. Of the 29 studies,[5,8,15,16,19–21,24–45] 14 studies (48.3%) reported the prevalence in the Europe, including 3 in France,[5,30,38] 3 in Germany,[19,31,43] 3 in Finland,[21,24,40] 2 in the UK,[36,41] 2 in Italy,[27,39] and 1 in Spain.[33] Six studies reported the prevalence in the Asia, including 3 in China[32,35,44] and 1 each in Japan,[8] Korea,[15] and Thailand.[34] Eight studies reported the prevalence in the United States[16,20,25,28,37,40,42,45] and 1 each study reported the prevalence in Madagascar,[27] Egypt,[29] and Latin America.[26] The worldwide prevalence map of ERP by region was shown in Fig. 1.

Twenty-four studies[15,16,19–21,24–27,30–34,36–45] have discussed sex differences in the incidence of ERP. Additionally, the main characteristics of the 14 articles[22,46–58] included physically active individuals were summarized in Table 2. The NOS quality assessment results were reported (see Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A162, Supplemental Content, which illustrates the risk of bias of included studies).

Table 1

Characteristics of the included studies to calculate total prevalence in the general population.

Study	Year	Total	Mean age	Population	Ethnicity	Region	Men%	ERP%	ERP of men (%)	ERP of women (%)
Holkeri[24]	2020	6631	50.1±13.9	Participants of the Mini-Finland Health Survey	Caucasian	Finland	44.5	12.0	14.6	9.8
Leiderman[25]	2020	17,901	53.0±13.0	Participants at Montefiore Medical center (n=6616)	AA	US	38.6	6.8	7.1	4.6
				Participants at Montefiore Medical center (n=9590)	Caucasian			4.9		
				Others	NA			4.5		
Matta[26]	2019	5398	35.0–74.0	A general population from four mid-sized cities of Latin America	NA	Latin America	41.3	7.3	9.2	5.9
Creta[27]	2019	616	7.5±2.7	Black African children from north-west Madagascar (300)	African	Madagascar	47.4	23.3	25.1	21.7
				Caucasian ethnicity individuals (316)	Caucasian	Italy		17.1	17.0	18.0
Trenkwalder[19]	2019	13,878	Mean: 54.6	A population-based cohort located in the Rhein-Main region	Caucasian	Germany	48.9	5.0	6.6	3.5
Hasegawa[8]	2019	395	<60.0	395 healthy controls	Asian	Japan	NA	10.0	NA	NA
Movahed[28]	2019	636	6.0–75.0	Participants from the Anthony Bates Foundation	NA	US	NA	13.5	NA	NA
Abdellah[29]	2018	1850	NA	Consecutive subjects who attended the outpatient clinic of cardiology and internal medicine at SCUH, Ismailia, Egypt	African	Egypt	NA	6.7	NA	NA
Kelly[20]	2018	4978	ERP (−):46.2–65.0 ERP (+): 43.2–62.7	Black in the Jackson Heart Study cohort	AA	US	35.8	28.3	50.2	16.1
Rohel[30]	2017	306	25.87±3.3	Female flight staff employed in French civilian or military sectors	Caucasian	France	0	9.2	NA	9.2
Trenkwalder[31]	2017	1630	51.3±13.5	Population-based Study of Health in Pomerania (SHIP-1)	Caucasian	Germany	47.1	4.8	5.1	4.5
Sun[32]	2017	10899	Mean: 53.6	The general rural Chinese population of Liaoning Province	Asian	China	45.3	1.3	2.6	0.2
Cho[15]	2017	26345	48±10.2	The general ambulatory Korean population from the Health Promotion Center of Asan Medical Center	Asian	Korea	60.6	11.2	15.3	4.8
Rodríguez-Capitán[33]	2017	13,179	Mean: 40	A large cohort of working adults aged 16–74 years in 5 cities in different regions of Spain	Caucasian	Spain	73.4	2.4	3.1	0.4
Makarawate[34]	2015	282	20.0–45.0	Healthy young northeastern Thai men at check-up clinics	Asian	Thailand	100.0	10.3	10.3	NA
Chen [35]	2014	2247	56.0±15.0	Adult who received an ECG during a physical checkup or in the outpatient clinics	Asian	China	47.9	24.2	NA	NA
Macfarlane[36]	2013	1496	≥18 .0	Healthy individuals in the authors' lab in UK	Caucasian	UK	57.4	29.3	35.0	21.5
Walsh[37]	2013	5069	18.0–30.0	Participants (40% black) from the CARDIA cohort (n=2028)	AA	US	45.5	30.5	36.6	3.5
				Participants (60% white) from the CARDIA cohort (n=3041)	Caucasian			10.6		
Rollin[38]	2012	1161	49.8±8.6	In middle-aged individuals living in the southwestern France	Caucasian	France	51.6	13.7	21.0	5.9
Lanza[39]	2012	4176	ERP (+): 38.3±17.9 ERP (−): 52.3±17.8	At Cardiology Service and the Center of pre-hospital evaluation of University Hospital in Italy (without structural heart disease)	Caucasian	Italy	45.0	2.0	3.7	0.6
Noseworthy[40]	2011	9444	18.0–80.0	Framingham Heart Study (n=3955)	Caucasian	US	45.0	4.5	7.6	2.0
				Health 2000 Study (n=5489) in Finland	Caucasian	Finland				
Reinhard[41]	2011	1877	18.0–60.0	1877 individuals from 505 white nuclear families	Caucasian	UK	50.2	7.7	11.7	3.7
Uberoi[42]	2011	29281	Male: 55.0±14.0 Female: 56.0±17.0	From the VA Palo Alto Health Care System (n=3875)	AA	US	87.2	6.0	2.5	0.6
				From the VA Palo Alto Health Care System (n=25,406)	Caucasian			1.7		
Tikkanen[21]	2011	10,864	30.0–59.0	Middle-aged from 35 different geographical areas of Finland	Caucasian	Finland	52.0	5.3	6.7	3.8
Sinner[43]	2010	6213	52.0±10.1	In the region of Augsburg, Southern Germany	Caucasian	Germany	48.8	13.1	14.5	11.7
Haissaguerre[5]	2008	412	36.0±12.0	Control group comprised 412 subjects without heart disease	Caucasian	France	65.5	5.1	NA	NA
Kui[44]	2008	1817	46.0±15.0	Healthy Chinese from April 2006 to July 2006	Asian	China	62.2	4.6	6.8	0.9
Klatsky[45]	2003	2081	24.0–62.0	Individuals undergoing health examinations (n=759)	AA	US	55.7	45.8	50.0	9.5
				Individuals undergoing health examinations (n=204)	Asian			35.8		
				Individuals undergoing health examinations (n=1,298)	Caucasian			19.2		
Surawicz[16]	2002	1073	5.0–96.0	Digitally stored ECGs, interpreted as normal, at St. Vincent Hospital, Indianapolis	Caucasian	US	49.3	31.5	53.3	10.3

AA=African American, CARDIA=coronary artery risk development in young adults, NA=not available.
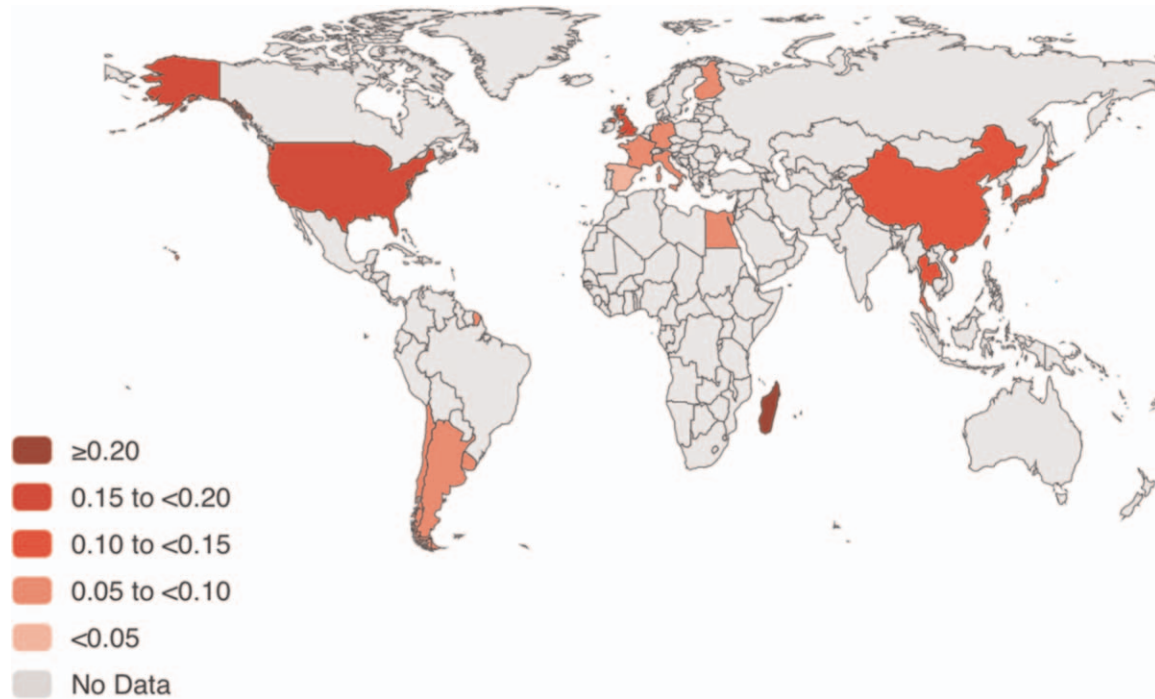
Figure 1. World prevalence map of ERP in the general population. ERP=early repolarization pattern.

Table 2

Characteristics of physically active individuals.

| Study	Year	Total	Mean age	Population	ERP%
Reinhard[22]	2019	623	21.0±5.0	Elite athletes who were examined in the outpatient clinic of the Department of Prevention and Sports Medicine, Technical University Munich, Germany.	17.3
Miragoli[46]	2019	414	13.6±1.8	Non-professional healthy adolescent athletes	22.2
Roche[47]	2018	2508	24.0±5.0	Recruits of the French Foreign Legion who were healthy and physically active men	19.5
Malhotra[48]	2015	66	NA	Actively training Indian athletes training for competitive sports in one of the premier training institutes of Indian Armed Forces between July 2012 and August 2012	42.4
Kiss[49]	2015	227	27.2±8.7	Asymptomatic elite, non-elite and master athletes in Hungarian	64.3
Brosnan[50]	2015	726	16.0−40.0	Non-Caucasian Australian male athletes (173) Caucasian male athletes (553)	36.8
Serra-Grima[51]	2015	299	ERP (+): 20.5±6.4 ERP (−): 20.1±6.4	White elite athletes recruited between 1960 and 1999	31.4
Vinsonneau[52]	2015	250	22.9±0.5	Healthy military officers aged over 17 years, Caucasians and practicing at least two hours of sport per week	19.2
Aagaard [53]	2014	151	50.0±5.0	Physically active middle-age males who had registered for first-time participation in the 2010 cross-country race and lived in the Greater Stockholm area	44.4
Vinsonneau[54]	2013	746	29.0±10.3	Caucasian military officers incorporated or engaged in French Navy units in Brittany from November 2010 to November 2011	13.8
Noseworthy[55]	2011	879	18.4±0.8	Student athletes ≥18 years old who were official participants in competitive inter-collegiate athletics between 2006 and 2010	25.1
Junttila[56]	2011	503	17.0−24.0	Athletes at the University of Miami in 2000	29.8
Ouali[57]	2011	540	18.3±2.4	Athletes in the Central Sports Medicine Centre of El Menzah in Tunisia, 100% white Arabs	22.0
Bianco[58]	2001	155	30.9±10.1	Top-ranking male Caucasian athletes	89.7

ERP = early repolarization pattern.
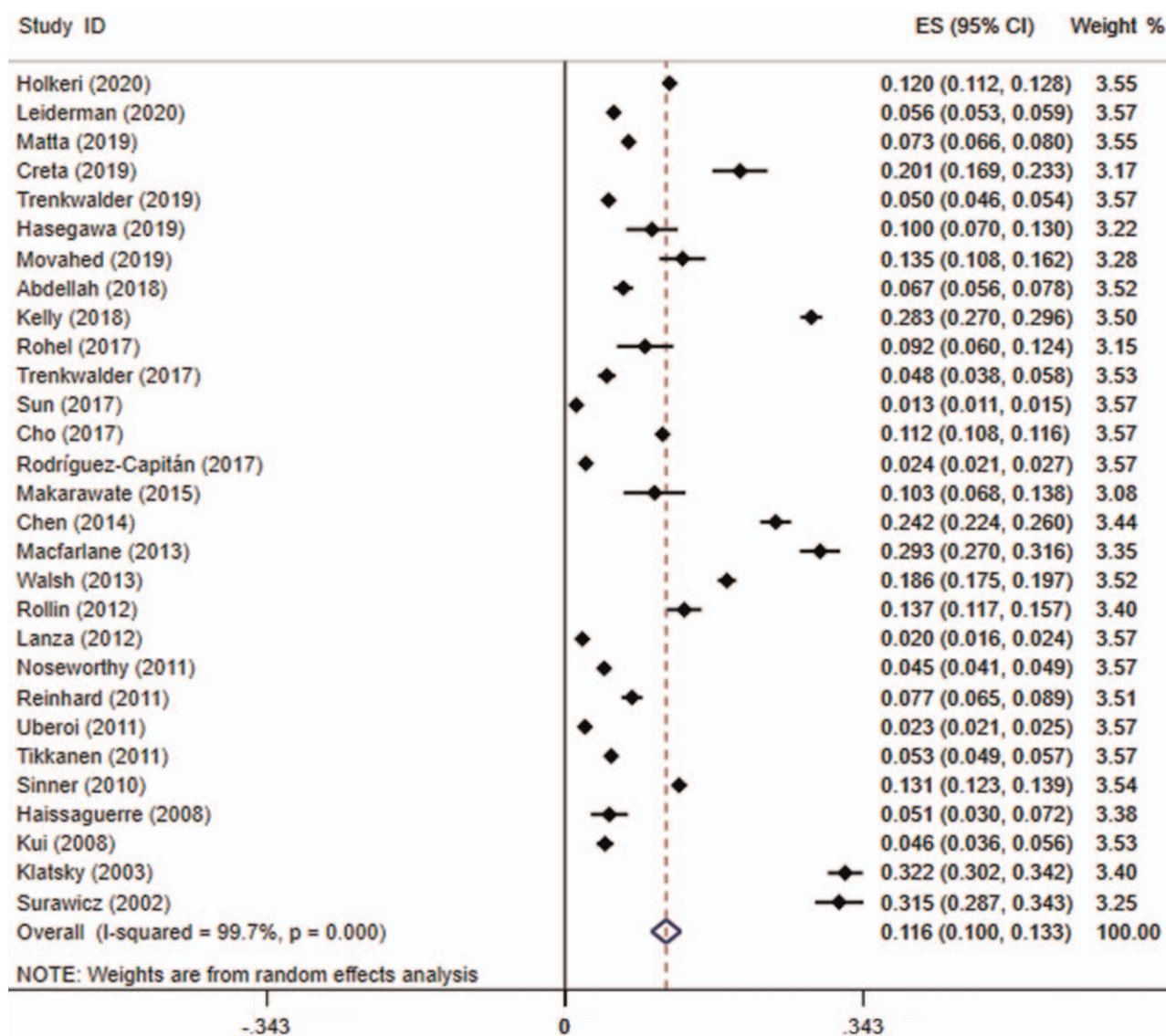
Figure 2. Forest plot of the prevalence of ERP in the general population. ERP = early repolarization pattern.

3.3. Prevalence of ERP and subgroup analyses

According to the 29 studies reported prevalence in general population, the worldwide pooled prevalence of ERP was 11.6% (95% CI: 10.0%–13.3%, Fig. 2) irrespective of age, sex, race, region, and country. There was a significant heterogeneity among these 29 studies (Cochran Q statistic's $P < .001$; $I^2 = 99.7\%$) and the sensitivity analysis was shown (see Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A154, Supplemental Content).

Twenty-four articles have studied the sex differences of the prevalence of ERP. The pooled prevalence of ERP in men was 17.0% (95% CI: 14.3%–19.6%, see Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A155, Supplemental Content) while that in the women was 6.2% (95% CI: 5.1%–7.3%, see Figure S4, Supplemental Digital Content, http://links.lww.com/MD/G174, Supplemental Content).

The prevalence of ERP in different races was also reported in the included studies. The results of racial prevalence of ERP were presented in Figures S5–S7, Supplemental Digital Content, http://links.lww.com/MD2/A158, http://links.lww.com/MD2/A159, http://links.lww.com/MD2/A160. The prevalence of ERP was 20.9% (95% CI: 13.1%–28.8%, see Figure S5, Supplemental Digital Content, http://links.lww.com/MD2/A158, Supplemental Content) in blacks, which was twice higher than the worldwide prevalence in the general population. And the incidence was 13.4% (95% CI: 7.9%–18.8%, see Figure S6, Supplemental Digital Content, http://links.lww.com/MD2/A159, Supplemental Content) in Asians and 10.1% (95% CI: 8.5%–11.7%, see Figure S7, Supplemental Digital Content, http://links.lww.com/MD2/A160, Supplemental Content) in Caucasians.

For the physically active individuals, including athletes and military officers, the mean prevalence of ERP was 33.9% (95% CI: 25.3%–42.6%, Fig. 3). The heterogeneity among these studies was statistically significant (Cochran Q statistic's $P < .001$; $I^2 = 98.8\%$). The sensitivity analysis was conducted (see Figure S8, Supplemental Digital Content, http://links.lww.com/MD2/A161, Supplemental Content), which didn't indicate obvious influence of each study on the overall result.
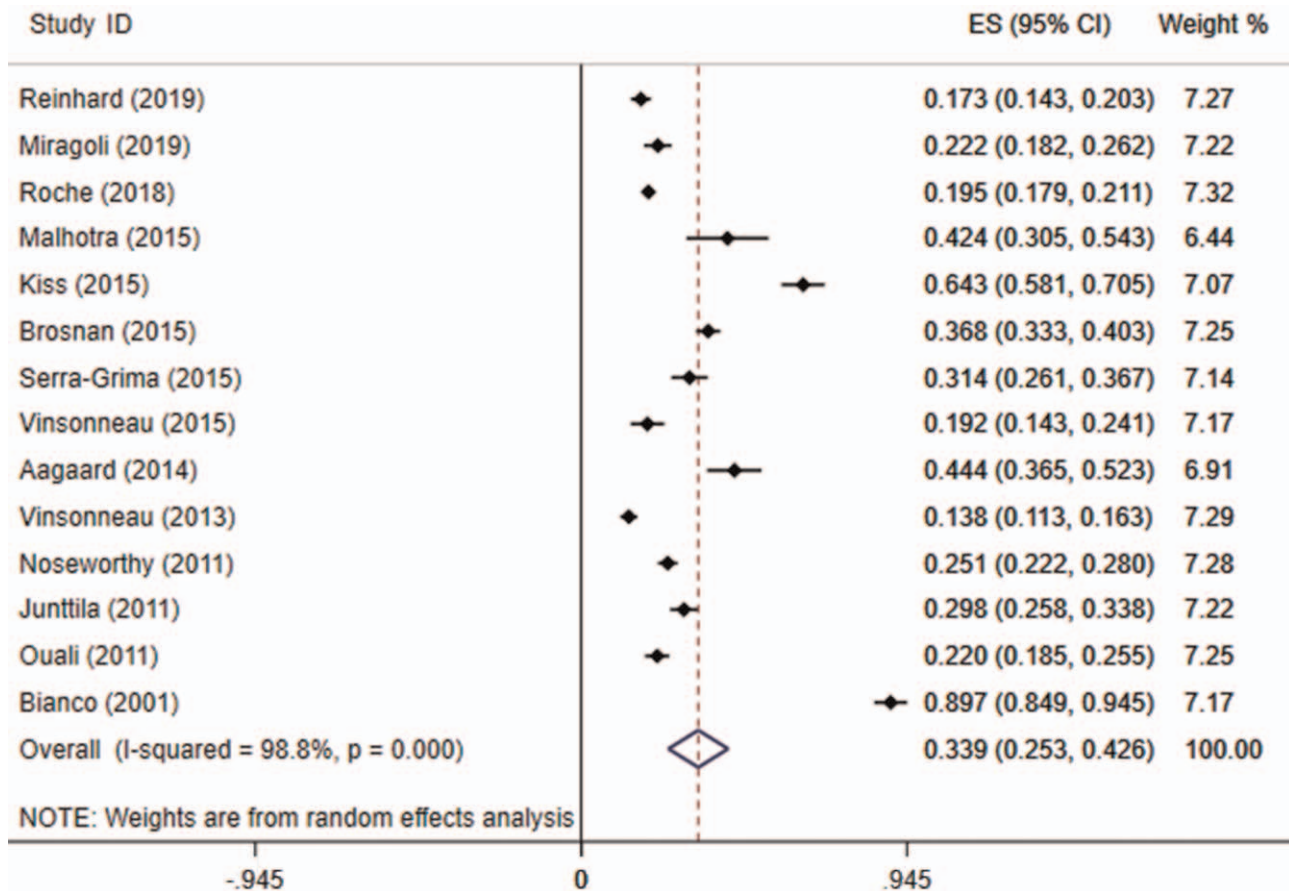
Figure 3. Forest plot of the prevalence of ERP in the physically active individuals. ERP = early repolarization pattern.

4. Discussion

The elevation of the J point ≥ 0.1 mV in at least 2 leads in the inferior (II, III, aVF) and/or lateral leads (I, aVL, V4–V6) is the main characteristic of ERP. Although ERP has been generally considered benign for decades, recent studies have indicated that ERP portends an increased risk of lone atrial fibrillation, idiopathic ventricular fibrillation, and sudden death without structural heart disease.[5–8] The present study is the first systematic review and meta-analysis to evaluate the worldwide prevalence of ERP among different sexes, ethnicities, regions, countries, and populations. The prevalence of ERP around the world in the general population is about 11.6%. There is a trend toward a higher frequency in blacks, men, and physically active individuals.

In this study, the incidence of ERP is 17.0% and 6.2% in men and women with 176,595 subjects included. The outcome is in keeping with Ezaki study, which has already reported sex differences in the incidence of various types of ventricular arrhythmias.[17] It has been known for years that the J point or ST onset is higher in men in all precordial leads.[4,17] This phenomenon might result from the effect of the male hormone testosterone.[17,59,60] On the other hand, the trans-membrane voltage gradient of action potential is triggered by transient outward potassium current (Ito)-activity in phase 1 and 2.[53] This gradient is the physiological basis of slur or notching of the ECG for ERP.[61] In normal subjects with different sex, there is always a small degree of heterogeneity in this voltage gradient.[17]

In summary, the effect of sex hormones and the heterogeneity in voltage gradient have been considered to be the physiological basis for sex differences in ERP.

According to our pooled analyzed prevalence, ERP is approximately twice as common in blacks as in Caucasians, which is similar to previous studies.[20,27,62] Olson et al reported that 24.4% of blacks versus 7.9% of whites had J-point elevation based on Atherosclerosis Risk in Communities (ARIC) study.[20,62] Considering correlation between ECG variations and body composition proposed in previous studies,[63,64] differences in body build, composition, and nutrition might in part explain the clinical differences in prevalence among races.[28]

The present study shows that ERP is more prevalent in physically active individuals (33.9%), which is in accordance with Tikkanen study.[21] According to Tikkanen research, the prevalence of ERP was 43.5% among the Finnish athletes and 30.0% among the US athletes.[21] Vinsonneau study also showed that ERP was more common in population that takes exercise regularly.[54] Vagotonia is often observed in physically active individuals and may increase regional electrophysiological differences and repolarization dispersion in the myocardium, which might explain the development of J-point elevation in athletes.[53,65,66]

However, our study has the following limitations: the subjects in our study are mostly from Europe, Asia, and US. There are only 2 studies from Africa and 1 study from Latin America. Another limitation of this study is the imbalance of the sex ratio

(100,467 men, 76,128 women), which may cause bias. The heterogeneity in the overall and subgroup analyses is also a limitation of this study. Heterogeneities in each analysis are high, likely because of differences in methodology, population, ethnicity, and geographic region.

5. Conclusions

In conclusion, according to our study the worldwide prevalence of ERP in the physically active individuals is much higher (around 33.9%) than in subjects from the general population (around 11.6%). The prevalence of ERP in men and blacks is higher as compared with others in the general population. These above-mentioned results might indicate that clinical screening and further examination of ERP in potential population need to be considered.

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Author contributions

Hong-Yan Ji and Xiao-Qing Quan contributed to the conception and design of this study. Hong-Yan Ji, Nan Hu and Rui Liu were involved in the selection of the included studies. Hong-Yan Ji, Nan Hu, Rui Liu, Hai-Rong Zhou, Wei-Liang Gao and Xiao-Qing Quan were involved in the acquisition and interpretation of the data. The manuscript was written and reviewed by Hong-Yan Ji, Nan Hu, Rui Liu, Hai-Rong Zhou, Wei-Liang Gao and Xiao-Qing Quan. All authors read and approved the final manuscript.
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Writing – review & editing: Xiao-Qing Quan.

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