European Child & Adolescent Psychiatry (2019) 28:1283–1293
https://doi.org/10.1007/s00787-018-1217-x

REVIEW

Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis

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Received: 18 May 2018 / Accepted: 21 August 2018 / Published online: 24 August 2018

Abstract

This meta-analysis was conducted to evaluate the association between Attention deficit hyperactivity disorder (ADHD) medications and risk of sudden death/arrhythmia, stroke, myocardial infarction as well as all-cause death. We searched PubMed, Web of Science and China National Knowledge Infrastructure from 1950 to May 2018. All observational studies that the exposure of interest was ADHD medications, the outcome of interest was sudden death/arrhythmia, stroke, myocardial infarction as well as all-cause death, and the study reported relative risks (RRs) with 95% confidence intervals (95% CIs) were included. Pooled RRs were estimated by random-effects model. Subgroup analyses were conducted to examine the effects of study design, population, Country, follow-up duration, female proportion, covariates adjustment on the risk of sudden death/arrhythmia. Eight articles with ten studies (4,221,929 participants) were included in this meta-analysis about the association between ADHD medications and risk of sudden death/arrhythmia. The pooled RRs with 95% CIs of sudden death/arrhythmia for ADHD medications were 1.39 (1.06, 1.83). The result of the cohort study was 1.24 (0.84, 1.83). The pooled RRs between ADHD medications and stroke, myocardial infarction, all-cause death were 1.00 (0.74, 1.35), 0.91 (0.79, 1.05), 0.89 (0.54, 1.45), respectively. As for methylphenidate, the pooled RRs between methylphenidate and sudden death/arrhythmia, stroke, myocardial infarction, all-cause death were 1.46 (1.03, 2.07), 0.92 (0.70, 1.21), 0.97 (0.77, 1.23), 1.00 (0.49, 2.04), respectively. Based on the results of cohort studies, there was no correlation between ADHD medications and sudden death/arrhythmia, stroke, myocardial infarction and all-cause death. However, some of the confidence intervals do not exclude modest elevated risks, e.g., for sudden death/arrhythmia.

Keywords ADHD medications · All-cause death · Meta-analysis · Myocardial infarction · Stroke · Sudden death/arrhythmia

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder that is characterized by hyperactivity, inattention, and impulsivity [1]. ADHD is a childhood-onset disorder, but symptoms may persist into adulthood [2]. In the United States, its prevalence in the childhood and adulthood was 2.2–17.8% [3] and 4–4.5% [4, 5], respectively. Clinical guidelines and practice parameters show that medications play a key role in the clinical management of ADHD [6–8]. The recommended medications of ADHD include stimulants (e.g., methylphenidate and amphetamines) and non-stimulant medications (e.g., atomoxetine) [9].

Drugs with the same pharmacological properties as amphetamine include methamphetamine, dextroamphetamine, amphetamine salt (https://www.fda.gov/drugs/drugsafety/ucm277770.htm). Because ADHD medications can rapidly reduce the overt clinical manifestations, it has rapid growth in the use of such agents [10].

However, two studies revealed that ADHD medications use among children and adults diagnosed with ADHD was associated with increasing of systolic blood pressure, diastolic blood pressure and heart rate [11, 12]. Furthermore, some studies have reported adverse events that included cases of sudden death, myocardial infarction, and stroke in conjunction with ADHD medications use [13].

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Accordingly, some observational studies have been conducted to assess the association between ADHD medications and the risk of sudden death/arrhythmia, stroke, myocardial infarction as well as all-cause death. Several studies indicated that ADHD medications can increase the risk of sudden death/arrhythmia [14–17]. However, other studies proposed no association between them [18–21]. In addition, the results are also inconsistent between ADHD medications and stroke, myocardial infarction and all-cause death [14, 15, 17–21]. Therefore, there continues to be a controversy about whether there exists an association between ADHD medications and sudden death/arrhythmia, stroke, myocardial infarction as well as all-cause death. So our meta-analysis seeks to estimate the strength of association between them.

Materials and methods

We referred to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of meta-analyses in this analysis [22].

Search strategy

Two investigators independently identified articles through a systematic search of PubMed, Web of Science and China National Knowledge Infrastructure from 1950 to May 2018, and by searching the reference lists of selected articles. The search terms were as following: (((((((((sudden death) OR sudden cardiac death) OR arrhythmia) OR ventricular arrhythmia) OR stroke) OR MI) OR Myocardial infarction) OR all-cause death)) AND ((((((((((((ADHD) OR attention deficit hyperactivity disorder)) AND ((((((therapy) OR treatment) OR drug) OR medicine) OR medications))) OR methylphenidate) OR dexmethylphenidate) OR methamphetamine) OR dextroamphetamine) OR amphetamine salts) OR amphetamine) OR pemoline) OR atomoxetine)).

Inclusion criteria

The inclusion criteria were as following: (1) observational study was published as the original study; (2) the exposure of interest was ADHD medications (methylphenidate, dexmethylphenidate, methamphetamine, dextroamphetamine, amphetamine salts, amphetamine, pemoline, atomoxetine); (3) the primary outcome of interest was sudden death/arrhythmia, and the secondary outcome of interest was stroke, myocardial infarction and all-cause death; The rationale for considering sudden cardiac death and arrhythmia as a composite outcome is that sudden cardiac death is often due to undocumented ventricular arrhythmia, and considered presumed arrhythmic death [18]. (4) the study reported RRs, odds ratios or hazard ratios with 95% CIs, with all results being presented as RRs; All selected studies were carefully checked by two investigators, respectively, to ensure that individual study was eligible for inclusion criteria in this meta-analysis. If the two investigators were disputable about the eligibility of an article, it was resolved by discussing with a third investigator.

Data extraction

Two investigators independently extracted the relevant data. If there are disagreements between them, it was resolved through discussion. Information extracted from each study was as follows: (1) the first author's name; (2) publication year; (3) country where the study was conducted; (4) age range of subjects; (5) female proportion; (6) study design; (7) years of follow up; (8) exposure classification; (9) outcome events; (10) sample size and number of cases; (11) RRs (we presented all results with RRs for simplicity) with corresponding 95% CIs; (12) variables adjusted for in the analysis.

Data synthesis

The random-effects model was used as the pooling method throughout the analysis. Pooled value was calculated as the inverse variance-weighted mean of the logarithm of RRs with 95% CIs to assess the strength of association between ADHD medications and the risk of sudden death/arrhythmia, stroke, myocardial infarction as well as all-cause death. We used the I^2 statistic to assess the heterogeneity between studies (I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively) [23]. Because the severity of ventricular arrhythmias and arrhythmias is different [24]. Sensitivity analysis was done to explore the effects of ADHD medications on arrhythmias of varying severity. Subgroup analyses were conducted to perform comparisons between groups. Meta-regression was performed to evaluate the potentially important covariates that might exert substantial impacts on between-study heterogeneity [25]. The leave-one-out sensitivity analysis [26] was also carried out to evaluate the key studies that have a substantial impact on the between-study heterogeneity. Influence analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study [27]. The Egger et al. [28] regression asymmetry test and the funnel plot were adopted to evaluate small-study effect. The Newcastle–Ottawa Quality Assessment scale (NOS) [29] was used to assess the overall quality and risk of bias of the observational studies.

All statistical analyses were performed with STATA version 15.0. All reported probabilities (P values) were two-sided with a statistical significance level of 0.05.

Results

Study selection and study characteristics

We identified 2472 articles by literature search. After exclusion of not for human being, not in English and Chinese, and duplicate articles, a total of 1868 articles were included for screening titles and abstracts. Another 1860 records were excluded for some reasons, and eight articles were included in this meta-analysis (Fig. 1). Eight articles containing ten studies with 4,221,929 participants provided results for ADHD medications and sudden death/arrhythmia. Seven articles containing eight studies with 3,274,486 participants provided results for ADHD medications and stroke. Five articles including six studies with 2,161,506 participants provided results regarding ADHD medications and myocardial infarction. Three articles including five studies with 2,831,293 participants provided results regarding ADHD medications and all-cause death.

As for methylphenidate, five articles containing six studies with 1,512,324 participants were for sudden death/arrhythmia, three articles containing three studies with 583,783 participants were for stroke, three articles containing three studies with 583,768 participants were for myocardial infarction and two articles containing three studies with 1,439,409 participants were for all-cause death. Detailed characteristics about the included studies appear in Table 1, Table 2. The methodological quality was assessed with the Newcastle–Ottawa scale. (Table 3).

Synthesis of results

The pooled RRs between ADHD medications and sudden death/arrhythmia were 1.39 (1.06, 1.83) (Fig. 2). When we excluded a study [16] (RR=7.4), the pooled RRs were 1.36 (1.04, 1.77). When we stratified studies by population, the pooled RRs in studies conducted in child and adult were 1.61 (1.49, 1.74) and 1.23 (0.77, 1.98), respectively. In subgroup analysis, the pooled RRs were 1.24 (0.84, 1.83) for cohort study, 1.21 (0.76, 1.92) for America, 1.13 (0.69, 1.85) for follow-up duration < 1 years, 1.62 (1.49, 1.75) for female proportion < 50%, and 1.21 (0.78, 1.87) for covariates adjusted age and gender. Because the severity of ventricular arrhythmias and arrhythmias is different. When we excluded two studies [14, 15] that the outcome was arrhythmia, the pooled RRs between ADHD medications and sudden death were 1.21 (0.76, 1.92).

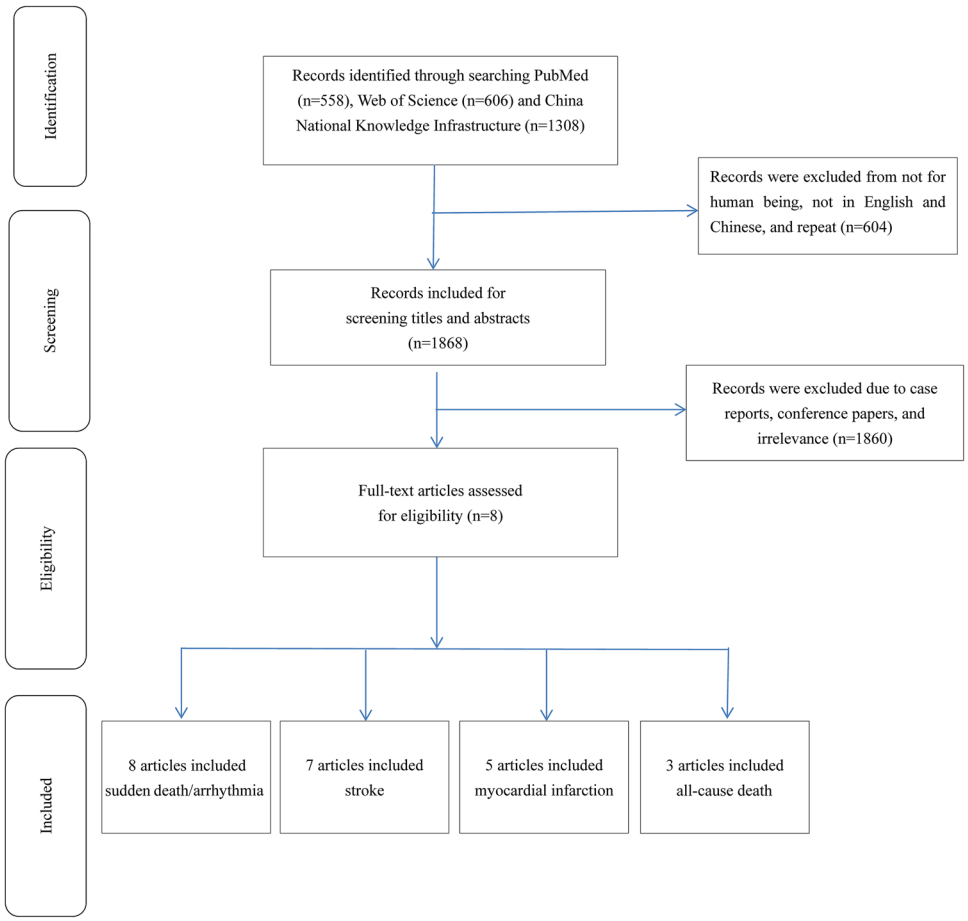

Fig. 1 Flowchart of the selection of studies included in the meta-analysis

Table 1 The detailed characteristics of the included studies for ADHD medications

Author (year)	Country	Population	Age (years)	Gender (female)	Study design	Years of follow-up	Exposure#	Outcome	Participant (cases)	RR (95% CI)	Adjustment for covariates
Schelleman H [18] 2013	America	Adults	> 18	54.10%	Cohort	Median 88 days	ADHD medications (Amphetamines)	Sudden death/ventricular arrhythmia	192,905 (NA)	1.18 (0.55, 2.54)	Propensity score[a]
								Stroke	192,905 (262)	0.80 (0.44,1.47)	
								Myocardial infarction	192,905 (322)	0.75 (0.42, 1.35)	
								All-cause death	192,905 (1080)	0.92 (0.71,1.19)	
Schelleman H [18] 2013	America	Adults	> 18	50.00%	Cohort	Median 60 days	ADHD medications (Atomoxetine)	Sudden death/ventricular arrhythmia	104,959 (NA)	0.41 (0.10, 1.75)	Propensity score[a]
								Stroke	104,959 (NA)	1.30 (0.52, 3.29)	
								Myocardial infarction	104,959 (NA)	0.56 (0.16,2.00)	
								All-cause death	104,959 (591)	0.50 (0.28, 0.89)	
Shin JY [14] 2016	Korea	Children and adolescents	< 17	22.00%	Case–control	4 years	ADHD medications (Methylphenidate)	Arrhythmia	864 (864)	1.61 (1.48,1.74)	Age, comorbidity[b] and comedication[c]
								Stroke	67 (10)	0.70 (0.49, 1.01)	
								Myocardial infarction	52 (10)	1.33 (0.90, 1.98)	
Huang MC [15] 2016	Taiwan	Adults	> 18	17.49%	Cohort	10 years	ADHD medications (Methamphetamine)	Arrhythmia	6575 (66)	1.92 (1.14, 3.22)	Propensity score[a]
								Stroke	6575 (183)	1.76 (1.28, 2.41)	
Gould MS [16] 2009	America	Children and adolescents	7–19	38.50%	Case–control	NA	ADHD medications (amphetamine, dextroamphetamine, methamphetamine, methylphenidate)	Sudden death	1128 (564)	7.40 (1.40, 74.90)	NA
Schelleman H [19] 2011 (primary)	America	Children and adolescents	3–17	27.80%	Cohort	Median 135 days	ADHD medications (amphetamine, atomoxetine, methylphenidate)	Sudden death/ventricular arrhythmia	1207,085 (NA)	1.60 (0.19, 13.60)	Data source
								All-cause death	1207,085(635)	0.76(0.52,1.12)	
Schelleman H [19] 2011 (secondary)	America	Children and adolescents	3–17	NA	Cohort	Median 210 days	ADHD medications (amphetamine, atomoxetine, methylphenidate)	Sudden death/ventricular arrhythmia	1,106,390 (NA)	1.43 (0.31, 6.61)	Data source
								Stroke	1,106,390 (NA)	0.89 (0.11, 7.11)	
								All-cause death	1,106,390 (535)	0.77 (0.56, 1.07)	
Cooper WO [21] 2011	America	Children and adolescents	2–24	29.00%	Cohort	Mean 2.10 years	ADHD medications (methylphenidate, dexmethylphenidate, dextroamphetamines, amphetamine salts, atomoxetine, pemoline)	Sudden cardiac death	938,871 (20)	0.88 (0.23, 3.35)	Site-specific propensity score decile, site, medical and psychiatric conditions[d], utilization variables[e], age, and calendar year
								Stroke	1,200,438 (30)	0.93 (0.29, 2.97)	
								Myocardial infarction	1,200,438 (9)	0.88 (0.16, 4.71)	

Table 1 (continued)

Author (year)	Country	Population	Age (years)	Gender (female)	Study design	Years of follow-up	Exposure#	Outcome	Participant (cases)	RR (95% CI)	Adjustment for covariates
Habel LA [20] 2011	America	Adults	25–64	54.00%	Cohort	Median 0.33 years	ADHD medications (methylphenidate, amphetamine, or atomoxetine)	Sudden cardiac death	443,198 (212)	0.80 (0.55, 1.18)	Site, age, sex, calendar year, and CRS[f]
								Stroke	443,198 (438)	0.76 (0.58, 1.00)	
								Myocardial infarction	443,198 (1059)	0.88 (0.74, 1.05)	
Schelleman H [17] 2012	America	Adults	> 18	55.40%	Cohort	Median 60 days	ADHD medications (Methylphenidate)	Sudden death/ventricular arrhythmia	219,954 (486)	1.84 (1.33, 2.55)	Propensity score[a]
								Stroke	219,954 (850)	1.14 (0.83, 1.56)	
								Myocardial infarction	219,954 (975)	0.87 (0.63, 1.21)	
								All-cause death	219,954 (8321)	1.74 (1.60, 1.89)	

ADHD attention deficit hyperactivity disorder, *CI* confidence interval, *NA* not available, *RR* relative risk

#All ADHD medications exposures are current users

[a]Demographic variables (age, gender, race, state, data source, calendar year, nursing home residence, an inpatient or outpatient claim) Diagnosis (acquired or hereditary anemia, adjustment disorder, alcohol use/abuse, anxiety, arrhythmia, asthma, autism, bipolar disease, chronic obstructive pulmonary disease, bronchitis cancer, capillaries disease, cardiomyopathy, cerebral degeneration, chromosomal abnormalities, conduct disorder, coagulation defects, congenital heart disease, cystic fibrosis, depression/depressive disorder, diabetes mellitus, electrocardiogram, emphysema, encopresis, enuresis, epilepsy, infantile cerebral palsy, human immunodeficiency virus, heart failure, hypercholesterolemia, hypertension, hypothyroidism, ischemic heart disease, kidney disease, learning disorder, liver disease, marfan syndrome, myocardial infarction, muscular dystrophy, narcolepsy, obesity, obsessive compulsive disorder, oppositional defiant disorder, osteoarthritis, osteogenesis imperfecta, other congenital malformations, other hereditary immune diseases, other metabolic disorders, psychosis, rheumatoid arthritis, sudden death/ventricular arrhythmia, smoking, stroke, tic disorder, valvular heart disease) Drugs[angiotensin-converting enzyme inhibitor, aldosterone inhibitor, Alpha-1 blocker, anorexient agent, antiadrenergic agent, antiarrhythmic agent, antidiabetic agent, antihyperlipidemic agent, antipsychotic dose, antiseizure agent, anxiolytic agent, aspirin, Beta-blocker, bronchodilator, bupropion, COX-2 inhibitors, calcium channel blocker, immunosuppressive agent, inhaled corticosteroid, inotropic agent, loop diuretic, non-steroidal anti-inflammatory agent, nitrate, oral corticosteroid, selective serotonin(-norepinephrine) reuptake inhibitor, thiazide diuretic, thyroid, tricyclic antidepressant, vasodilators, warfarin, xanthine derivate]

[b]Depressive episode, tic disorders, emotional disorders with onset specific to childhood, manic episodes, bipolar affective disorders, and mental retardation

[c]Atomoxetine, antipsychotics, antidepressants, anxiolotics, antiepileptics, and anticholinergic agents

[d]Serious cardiovascular disease, serious chronic illness, major psychiatric illness, substance abuse, antipsychotic use

[e]Medical hospitalization and general medical care access

[f]Mental health claims(major depression, bipolar disorder, anxiety, psychotic disorders) other selected medical conditions(ETOH/substance abuse, suicide attempt, injury, seizure, asthma) use of psychotropic medications(antipsychotic, tricyclic antidepressant, antidepressants, other or SSRI/SNRI, benzodiazepines, lithium, modafinil, insomnia medications, thioridazine, mood stabilizers, w/o seizure, Clonidine/guanfacine, w/o HT) use of other selected medications(beta-agonist, epinephrine, asthma medications, seizure medications, theophylline compounds, COX-2 inhibitors, other drugs to improve blood flow, clonidine, pde5 inhibitors, triptans, oral contraceptives, hormones, menopausal)

Table 2 The detailed characteristics of the included studies for methylphenidate

Author (year)	Country	Population	Age (years)	Gender (female)	Study design	Years of follow-up	Exposure#	Outcome	Participant(cases)	RR (95% CI)	Adjustment for covariates
Shin JY [14] 2016	Korea	Children and adolescents	< 17	22.00%	Case–control	4 years	Methylphenidate	Arrhythmia	864 (864)	1.61 (1.48, 1.74)	Age, comorbidity[a] and comedication[b]
								Stroke	67 (10)	0.70 (0.49, 1.01)	
								Myocardial infarction	52 (10)	1.33 (0.90, 1.98)	
Gould MS [16] 2009	America	Children and adolescents	7–19	38.50%	Case–control	NA	Methylphenidate	Sudden death	1128 (564)	13.50 (1.70, 618.00)	NA
Schelleman H [19] 2011 (primary)	America	Children and adolescents	3–17	27.80%	Cohort	Median 135 days	Methylphenidate	Sudden death/ventricular arrhythmia	640,585 (NA)	2.63 (0.29, 23.69)	Data source
								All-cause death	640,585 (NA)	0.61 (0.30, 1.25)	
Schelleman H [19] 2011 (secondary)	America	Children and adolescents	3–17	NA	Cohort	Median 210 days	Methylphenidate	Sudden death/ventricular arrhythmia	578,870 (NA)	1.30 (0.15, 11.14)	Data source
								All-cause death	578,870 (285)	0.79 (0.48, 1.29)	
Habel LA [20] 2011	America	Adults	25–64	54.00%	Cohort	Median 0.33 years	Methylphenidate	Sudden cardiac death	70,923 (193)	0.67 (0.38, 1.18)	Site, age, sex, calendar year, and CRS[c]
								Stroke	363,762 (414)	0.94 (0.68, 1.32)	
								Myocardial infarction	363,762 (984)	0.89 (0.71, 1.13)	
Schelleman H [17] 2012	America	Adults	> 18	55.40%	Cohort	Median 60 days	Methylphenidate	Sudden death/ventricular arrhythmia	219,954 (486)	1.84 (1.33, 2.55)	Propensity score[d]
								Stroke	219,954 (850)	1.14 (0.83, 1.56)	
								Myocardial infarction	219,954 (975)	0.87 (0.63, 1.21)	
								All-cause death	219,954 (8321)	1.74 (1.60, 1.89)	

ADHD attention deficit hyperactivity disorder, *CI* confidence interval, *NA* not available, *RR* relative risk

#All ADHD medications exposures are current users

[a]Depressive episode, tic disorders, emotional disorders with onset specific to childhood, manic episodes, bipolar affective disorders, and mental retardation

[b]Atomoxetine, antipsychotics, antidepressants, anxiolotics, antiepileptics, and anticholinergic agents

[c]Mental health claims(major depression, bipolar disorder, anxiety, psychotic disorders) other selected medical conditions(ETOH/substance abuse, suicide attempt, injury, seizure, asthma) use of psychotropic medications(antipsychotic, tricyclic antidepressant, antidepressants, other or SSRI/SNRI, benzodiazepines, lithium, modafinil, insomnia medications, thioridazine, mood stabilizers, w/o seizure, Clonidine/guanfacine, w/o HT) use of other selected medications(beta-agonist, epinephrine, asthma medications, seizure medications, theophylline compounds, COX-2 inhibitors, other drugs to improve blood flow, clonidine, pde5 inhibitors, triptans, oral contraceptives, hormones, menopausal)

[d]Demographic variables (age, gender, race, state, data source, calendar year, nursing home residence, an inpatient or outpatient claim) Diagnosis (acquired or hereditary anemia, adjustment disorder, alcohol use/abuse, anxiety, arrhythmia, asthma, autism, bipolar disease, chronic obstructive pulmonary disease, bronchitis cancer, capillaries disease, cardiomyopathy, cerebral degeneration, chromosomal abnormalities, conduct disorder, coagulation defects, congenital heart disease, cystic fibrosis, depression/depressive disorder, diabetes mellitus, electrocardiogram, emphysema, encopresis, enuresis, epilepsy, infantile cerebral palsy, human immunodeficiency virus, heart failure, hypercholesterolemia, hypertension, hypothyroidism, ischemic heart disease, kidney disease, learning disorder, liver disease, marfan syndrome, myocardial infarction, muscular dystrophy, narcolepsy, obesity, obsessive compulsive disorder, oppositional defiant disorder, osteoarthritis, osteogenesis imperfecta, other congenital malformations, other hereditary immune diseases, other metabolic disorders, psychosis, rheumatoid arthritis, sudden death/ventricular arrhythmia, smoking, stroke, tic disorder, valvular heart disease) Drugs(angiotensin-converting enzyme inhibitor, aldosterone inhibitor, Alpha-1 blocker, anorexient agent, antiadrenergic agent, antiarrhythmic agent, antidiabetic agent, antihyperlipidemic agent, antipsychotic dose, antiseizure agent, anxiolytic agent, aspirin, Beta-blocker, bronchodilator, bupropion, COX-2 inhibitors, calcium channel blocker, immunosuppressive agent, inhaled corticosteroid, inotropic agent, loop diuretic, non-steroidal anti-inflammatory agent, nitrate, oral corticosteroid, selective serotonin(-norepinephrine) reuptake inhibitor, thiazide diuretic, thyroid, tricyclic antidepressant, vasodilators, warfarin, xanthine derivate)

Table 3 Quality assessment of studies included in the meta-analysis

ID	First author	Year	Selection	Quality assessment criteria		
				Comparability	Exposure (outcome)	Overall quality
1	Schelleman H (Amphetamines)	2013	****	**	**	8
2	Schelleman H (Atomoxetine)	2013	****	**	**	8
3	Shin JY (Methylphenidate)	2016	**	**	***	7
4	HuangMC (Methamphetamine)	2016	****	**	**	8
5	Gould MS[a]	2009	***	**	**	7
6	Schelleman H[b]	2011	****	**	*	7
7	Schelleman H[b]	2011	****	**	*	7
8	Cooper WO[c]	2011	****	**	**	8
9	Habel LA[b]	2011	****	**	**	8
10	Schelleman H (Methylphenidate)	2012	****	**	**	8

* represents one point

, *, **** indicates the score of each part

[a]Amphetamine, dextroamphetamine, methamphetamine, methylphenidate

[b]Amphetamine, atomoxetine, methylphenidate

[c]Methylphenidate, dexmethylphenidate, dextroamphetamines, amphetamine salts, atomoxetine, pemoline

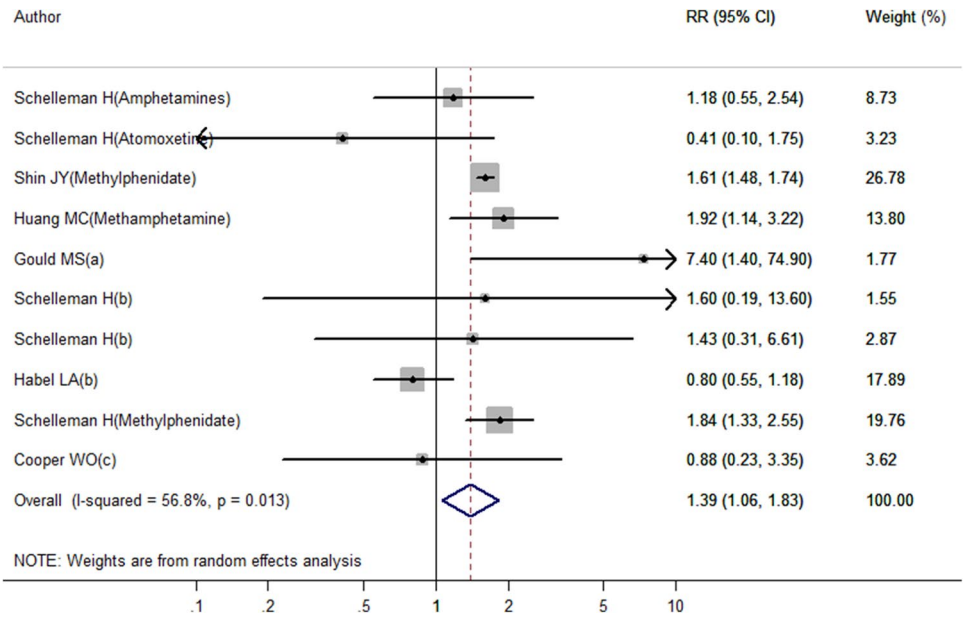

Fig. 2 Forest plot of ADHD medications and the risk of sudden death/arrhythmia. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals. a Amphetamine, dextroamphetamine, methamphetamine, methylphenidate. b Amphetamine, atomoxetine, methylphenidate. c Methylphenidate, dexmethylphenidate, dextroamphetamines, amphetamine salts, atomoxetine, pemoline

The pooled RR between ADHD medications and stroke was 1.00 (0.74, 1.35). In subgroup analysis, the pooled RRs were 1.08 (0.78, 1.50) for cohort study, 0.91 (0.75, 1.09) for America, 1.09 (0.75, 1.58) for adult. The pooled RRs between ADHD medications and myocardial infarction, all-cause death were 0.91 (0.79, 1.05), 0.89 (0.54, 1.45), respectively.

As for methylphenidate, the pooled RRs between methylphenidate and sudden death/arrhythmia, stroke, myocardial infarction, all-cause death were 1.46 (1.03, 2.07), 0.92 (0.70, 1.21), 0.97 (0.77, 1.23) and 1.00 (0.49, 2.04), respectively. The results of the pooled analysis are summarized in Table 4.

Sources of heterogeneity

A univariate meta-regression analysis was conducted to explore the between-study heterogeneity among ADHD medications and sudden death/arrhythmia. The results showed that the covariates of publication year ($P=0.427$), country where the studies were conducted ($P=0.298$), study design ($P=0.326$), sample size ($P=0.231$) were not the source of heterogeneity.

Table 4 Summary risk estimates of the association between ADHD medications, methylphenidate and risk of sudden death/arrhythmia as well as stroke, myocardial infarction, all-cause death

Exposure	Outcome	Subgroup	No. of studies	Pooled RR (95% CI)	I^2 (%)	*P* value
ADHD medications	Sudden death/arrhythmia	All studies	10	1.39 (1.06, 1.83)	56.80	0.013
		Sensitivity analysis				
		Sudden death (excluding arrhythmia)	8	1.21 (0.76,1.92)	57.40	0.022
		Study design				
		Cohort study	8	1.24 (0.84, 1.83)	55.30	0.029
		Case–control study	2	2.46 (0.64, 9.41)	55.60	0.004
		Population				
		Child	5	1.61 (1.49, 1.74)	0.00	0.548
		Adult	5	1.23 (0.77, 1.98)	73.80	0.004
		Country				
		America	8	1.21 (0.76, 1.92)	57.40	0.022
		Non-America	2	1.62 (1.49, 1.75)	0.00	0.511
		Follow-up duration				
		> 1 years	3	1.61 (1.49, 1.75)	0.00	0.543
		< 1 years	6	1.13 (0.69, 1.85)	61.90	0.022
		Female proportion				
		> 50%	3	1.21 (0.67, 2.21)	81.20	0.005
		< 50%	5	1.62 (1.49, 1.75)	0.00	0.483
		Covariates adjustment				
		Adjust age and gender	6	1.21 (0.78, 1.87)	68.00	0.008
		Non-adjust age and gender	3	1.61 (1.48, 1.74)	0.00	0.989
	All-cause death	All studies	5	0.89 (0.54, 1.45)	94.10	0.000
	Stroke	All studies	8	1.00 (0.74, 1.35)	67.30	0.003
	Myocardial infarction	All studies	6	0.91 (0.79, 1.05)	0.00	0.445
Methylphenidate	Sudden death/arrhythmia	All studies	6	1.46 (1.03, 2.07)	58.50	0.034
	All-cause death	All studies	3	1.00 (0.49, 2.04)	88.50	0.000
	Stroke	All studies	3	0.92 (0.70, 1.21)	49.70	0.137
	Myocardial infarction	All studies	3	0.97 (0.77, 1.23)	40.80	0.185

ADHD attention deficit hyperactivity disorder, *CI* confidence interval, *RR* relative risk

One study [20] was found to be key contributors to this moderate between-study heterogeneity by the leave-one-out sensitivity analysis. After excluding this study, low heterogeneity (I^2 = 3.4%, $P_{heterogeneity}$ = 0.406) was found, and the pooled RRs were 1.62 (95% CIs 1.45 to 1.81).

A univariate meta-regression analysis was also conducted to explore the between-study heterogeneity among ADHD medications and stroke. The results showed that the covariates of publication year (P = 0.527), country where the studies were conducted (P = 0.603), study design (P = 0.311), sample size (P = 0.568) were not the source of heterogeneity.

Influence analysis and small-study effect

In influence analysis, no individual study was found to have an excessive influence on the pooled effect in influence analysis for ADHD medications and sudden death/arrhythmia (Fig. 3). The pooled RRs (95% CIs) ranged from 1.29 (0.90,

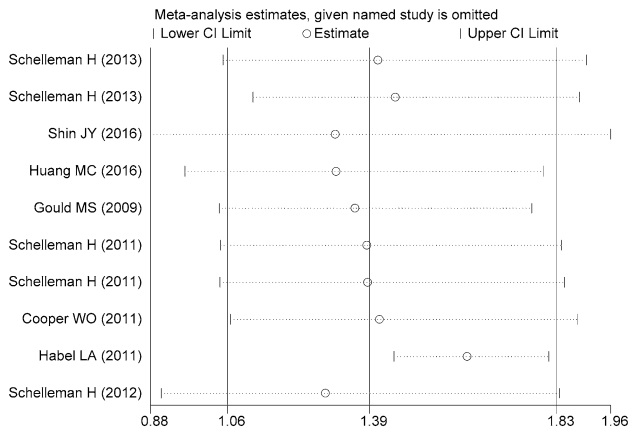

Fig. 3 Influence analysis of the included studies for ADHD medications and the risk of sudden death/arrhythmia. The middle line represents the pooled effect value. The bilateral lines represent 95% confidence interval

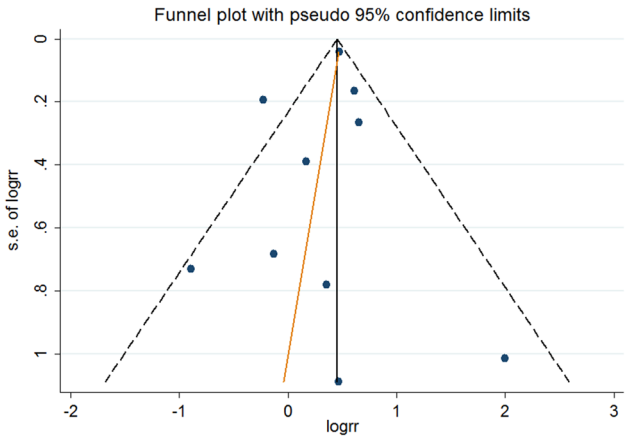

Fig. 4 The funnel plot of ADHD medications and the risk of sudden death/arrhythmia. Each dot represents a different study

1.84) to 1.62 (1.45, 1.81). The visual inspection of the funnel plot and Egger's test ($P=0.443$) showed no evidence of publication bias for all included studies (Fig. 4).

No individual study was found to have an excessive influence on the pooled effect in influence analysis among ADHD medications and stroke. The pooled RRs (95% CIs) ranged from 0.86 (0.73, 1.01) to 1.08 (0.78, 1.49). The visual inspection of the funnel plot and Egger's test ($P=0.970$) showed no evidence of publication bias for all included studies for stroke.

Discussion

Our meta-analysis based on ten studies including 4,221,929 participants showed a positive association between ADHD medications and risk of sudden death/arrhythmia. A meta-analysis (three studies, 1,884,963 patients) in 2013s conducted by Marianna Mazza [30] showed inconsistent conclusions. Because this meta-analysis only contained three studies (1,884,963 patients), fewer participants resulted in inconsistent results with our study and decreased the power of test. Our study failed to confirm the relationship between ADHD medications and stroke, myocardial infarction, all-cause death. The single methylphenidate user showed the positive association with the risk of sudden death/arrhythmia, but the association between methylphenidate and stroke, myocardial infarction, all-cause death was no statistical significance.

Not a single factor but various factors conjointly account for the impact of ADHD medications on cardiovascular diseases. ADHD medications (both stimulants and atomoxetine) have the same pharmacological properties to produce cardiovascular effects by increasing heart rate and blood pressure. For each type of ADHD drug, the situation is slightly different. Methylphenidate and amphetamines are sympathomimetic agents that stimulate the release of catecholamine [31], which increase heart rate and blood pressure. A similar assay can be applied to atomoxetine, a selective norepinephrine reuptake inhibitor that is used in ADHD therapy since 2003. It has been calculated that these agents can increase systolic and diastolic blood pressures (on average 1–4 mmHg) and heart rate (on average 3–8 bpm) [19]. And a meta-analysis concluded that an increment in resting heart rate can increase the risk of sudden death [32]. High resting heart rate increases the risk of sudden death that results from ventricular fibrillation [33].

Furthermore, increased blood pressure was related to an increased risk of sudden death/arrhythmia in a prospective population-based study [34]. Increased blood pressure is an independent risk factor for coronary artery disease. It has been documented that hypertension and coronary artery disease predisposes to left ventricular hypertrophy, which has been shown to increase the risk of arrhythmias and sudden cardiac death [35–37]. Meanwhile, high blood pressure also accelerates the process of plaque rupture that may lead to sudden death/arrhythmia [38, 39]. All these effects predispose users to a higher risk of sudden death/arrhythmia.

Our meta-analysis showed moderate between-study heterogeneity. A univariate meta-regression analysis with the covariates of publication year, country where the studies were conducted, study design, sample size was conducted to explore the between-study heterogeneity among ADHD medications and sudden death/arrhythmia. However, no source of heterogeneity was identified.

One study [20] was found to be key contributors to this moderate between-study heterogeneity by the leave-one-out sensitivity analysis. After excluding this study, the heterogeneity was low, and the results were found to be consistent with the one based on all studies, indicating that our results were stable and reliable. The reasons why this article contributes to moderate heterogeneity may be as follows: First, the subject age of this study [20] was large. Second, this study used an ICD-9/10 code-based definition for outcome, which may generate misclassification of some outcome. Third, confounders adjusted for in each study were different. The confounders (e.g., the medical status and drugs use) adjusted in this study were not completely consistent with other studies. Forth, the proportion of each single drug used is different. All these factors combined to contribute to the between-study heterogeneity.

A major strength of the present meta-analysis is a larger number of participants included, allowing a much greater possibility of reaching reasonable conclusions. Second, nearly all included studies had adjusted for potential confounders (e.g., age, gender, data source) increasing the credibility of the results. Third, our study analyzed the association between ADHD medications and four

cardiovascular diseases (sudden death/arrhythmia, stroke, myocardial infarction as well as all-cause death), indicating a multifaceted relationship between them.

This study has some limitations. First, the diagnosis in the claims data was coded based on the ICD-9-CM or ICD-10-CM System, and misclassification of some cases may have occurred. Second, confounders adjusted for in each study were different and there are some additional unknown confounders that might result in residual confounding. Third, some studies with respect to duration, dosage, and route of ADHD administration were not available in the studies. Thus, we were unable to investigate any possible dose–response relationship between ADHD medications and outcome measures. Fourth, because of the limited study number, we could not analyze the relationship between any single medication and the outcome interest. Fifth, because of the small number of studies included in some subgroup analysis, the conclusions of some subgroups are unstable.

Conclusions and implications

In summary, based on the results of cohort studies, there was no correlation between ADHD medications and sudden death/arrhythmia, stroke, myocardial infarction and all-cause death. However, some of the confidence intervals do not exclude modest elevated risks, e.g., for sudden death/arrhythmia. With the increased use of drugs for ADHD globally, the benefits of ADHD medications should be carefully weighed against the potential cardiovascular diseases risk. Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of Interest The authors report no financial or other relationship relevant to the subject of this article.

Ethical standards The manuscript does not contain clinical studies or patient data.

References

1. Childress AC, Berry SA (2012) Pharmacotherapy of attention-deficit hyperactivity disorder in adolescents. Drugs 72(3):309–325. https://doi.org/10.2165/11599580-000000000-00000
2. Sharma A, Couture J (2014) A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother 48(2):209–225. https://doi.org/10.1177/1060028013510699
3. Skounti M, Philalithis A, Galanakis E (2007) Variations in prevalence of attention deficit hyperactivity disorder worldwide. Eur J Pediatr 166(2):117–123. https://doi.org/10.1007/s00431-006-0299-5
4. Modesto-Lowe V, Meyer A, Soovajian V (2012) A clinican's guide to adult attention-deficit hyperactivity disorder. Conn Med 76(9):517–523
5. Advokat C (2010) What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). Neurosci Biobehav Rev 34(8):1256–1266. https://doi.org/10.1016/j.neubiorev.2010.03.006
6. Pliszka S (2007) Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 46(7):894–921. https://doi.org/10.1097/chi.0b013e318054e724
7. Taylor E, Dopfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Rothenberger A, Sonuga-Barke E, Steinhausen HC, Zuddas A (2004) European clinical guidelines for hyperkinetic disorder—first upgrade. Eur Child Adolesc Psychiatry 13(Suppl 1):I7–I30. https://doi.org/10.1007/s00787-004-1002-x
8. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, Danckaerts M, Dopfner M, Faraone SV, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke EJ, Taylor E (2006) Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 15(8):476–495. https://doi.org/10.1007/s00787-006-0549-0
9. Hammerness PG, Surman CB, Chilton A (2011) Adult attention-deficit/hyperactivity disorder treatment and cardiovascular implications. Curr Psychiatry Rep 13(5):357–363. https://doi.org/10.1007/s11920-011-0213-3
10. Faraone SV, Glatt SJ (2010) A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry 71(6):754–763. https://doi.org/10.4088/JCP.08m04902pur
11. Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M, Dittmann RW, Hollis C, Kovshoff H, McCarthy S, Nagy P, Sonuga-Barke E, Wong IC, Zuddas A, Rosenthal E, Buitelaar JK (2017) Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD: a systematic review and meta-analysis of trials of methylphenidate, amphetamines and atomoxetine. CNS Drugs 31(3):199–215. https://doi.org/10.1007/s40263-017-0410-7
12. Mick E, McManus DD, Goldberg RJ (2013) Meta-analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. Eur Neuropsychopharmacol 23(6):534–541. https://doi.org/10.1016/j.euroneuro.2012.06.011
13. Nissen SE (2006) ADHD drugs and cardiovascular risk. N Engl J Med 354(14):1445–1448. https://doi.org/10.1056/NEJMp068049
14. Shin JY, Roughead EE, Park BJ, Pratt NL (2016) Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. BMJ 353:i2550. https://doi.org/10.1136/bmj.i2550
15. Huang MC, Yang SY, Lin SK, Chen KY, Chen YY, Kuo CJ, Hung YN (2016) Risk of cardiovascular diseases and stroke events in methamphetamine users: a 10-year follow-up study. J Clin Psychiatry 77(10):1396–1403. https://doi.org/10.4088/JCP.15m09872
16. Gould MSWB, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T (2009) Sudden death and use of stimulant medications in youths. Am J Psychiatry 166(9):992–1001
17. Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, Cziraky MJ, Strom BL, Hennessy S (2012) Methylphenidate and risk of serious cardiovascular events in adults.

Am J Psychiatry 169(2):178–185. https://doi.org/10.1176/appi.ajp.2011.11010125
18. Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, Cziraky MJ, Strom BL, Hennessy S (2013) Amphetamines, atomoxetine and the risk of serious cardiovascular events in adults. PLoS One 8(1):e52991. https://doi.org/10.1371/journal.pone.0052991
19. Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, Daniel GW, Cziraky MJ, Hennessy S (2011) Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics 127(6):1102–1110. https://doi.org/10.1542/peds.2010-3371
20. Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG, Cheetham TC, Quinn VP, Dublin S, Boudreau DM, Andrade SE, Pawloski PA, Raebel MA, Smith DH, Achacoso N, Uratsu C, Go AS, Sidney S, Nguyen-Huynh MN, Ray WA, Selby JV (2011) ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA 306(24):2673–2683. https://doi.org/10.1001/jama.2011.1830
21. Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST, Fireman BH, Fish FA, Kirshner HS, O'Duffy A, Connell FA, Ray WA (2011) ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 365(20):1896–1904. https://doi.org/10.1056/NEJMoa1110212
22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
24. Goel R, Srivathsan K, Mookadam M (2013) Supraventricular and ventricular arrhythmias. Prim Care 40(1):43–71. https://doi.org/10.1016/j.pop.2012.11.002
25. Higgins JP, Thompson SG (2004) Controlling the risk of spurious findings from meta-regression. Stat Med 23(11):1663–1682. https://doi.org/10.1002/sim.1752
26. Patsopoulos NA, Evangelou E, Ioannidis JP (2008) Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 37(5):1148–1157. https://doi.org/10.1093/ije/dyn065
27. Tobias A (1999) Assessing the influence of a single study in the meta-analysis estimate. Stata Tech Bull 8(47):15–17
28. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
29. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605. https://doi.org/10.1007/s10654-010-9491-z
30. Mazza M, D'Ascenzo F, Davico C, Biondi-Zoccai G, Frati G, Romagnoli E, Bassi B, Janiri L, Moretti C, Gaita F (2013) Drugs for attention deficit-hyperactivity disorder do not increase the mid-term risk of sudden death in children: a meta-analysis of observational studies. Int J Cardiol 168(4):4320–4321. https://doi.org/10.1016/j.ijcard.2013.04.169
31. Volkow ND, Wang GJ, Fowler JS, Molina PE, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas NR, Zhu W, Swanson JM (2003) Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. Psychopharmacology 166(3):264–270. https://doi.org/10.1007/s00213-002-1340-7
32. Zhang D, Wang W, Li F (2016) Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. CMAJ 188(15):E384–e392. https://doi.org/10.1503/cmaj.160050
33. Gopinathannair R, Martins JB (2008) Predicting sudden cardiac death in healthy humans: is there more to autonomic balance than we know? Heart Rhythm 5(2):306–307. https://doi.org/10.1016/j.hrthm.2007.10.038
34. Laukkanen JA, Jennings JR, Kauhanen J, Makikallio TH, Ronkainen K, Kurl S (2012) Relation of systemic blood pressure to sudden cardiac death. Am J Cardiol 110(3):378–382. https://doi.org/10.1016/j.amjcard.2012.03.035
35. Ghali JK, Kadakia S, Cooper RS, Liao YL (1991) Impact of left ventricular hypertrophy on ventricular arrhythmias in the absence of coronary artery disease. J Am Coll Cardiol 17(6):1277–1282
36. Siegel D, Cheitlin MD, Black DM, Seeley D, Hearst N, Hulley SB (1990) Risk of ventricular arrhythmias in hypertensive men with left ventricular hypertrophy. Am J Cardiol 65(11):742–747
37. Szlachcic J, Tubau JF, O'Kelly B, Ammon S, Daiss K, Massie BM (1992) What is the role of silent coronary artery disease and left ventricular hypertrophy in the genesis of ventricular arrhythmias in men with essential hypertension? J Am Coll Cardiol 19(4):803–808
38. Burke AP, Farb A, Malcom GT, Liang Y, Smialek JE, Virmani R (1999) Plaque rupture and sudden death related to exertion in men with coronary artery disease. JAMA 281(10):921–926
39. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R (1997) Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 336(18):1276–1282. https://doi.org/10.1056/nejm199705013361802