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Acupuncture related adverse events – systematic review and meta-analyses of prospective clinical trials

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Abstract

Objective

Overview on risks for acupuncture related adverse events (AE).

Design

Systematic review and meta-analysis of prospective studies.

Data sources

Pubmed, Scopus, and EMBASE from inception date to September 15, 2019.

Eligibility criteria for selecting studies

Prospective studies assessing AE caused by needle acupuncture in humans as primary outcome published in English or German

Data extraction and synthesis

Two independent researchers selected articles, extracted the data and assessed study quality. Overall risks and risks for different AE categories were obtained from random effects meta-analyses.

Main outcomes

Overall risk for minor AE and serious AE (SAE) per patients and per treatments

Results

Out of 7679 screened articles 22 reporting on 21 studies were included. Meta-analyses suggest at least one AE occurring in 9.31% (95%-CI 5.10 to 14.62; 11 studies) of patients undergoing an acupuncture series and in 7.57% (95%-CI 1.43 to 17.95; 5 studies) of treatments. Summary risk estimates for SAE were 1.01 (95%-CI 0.23 to 2.33; 11 studies) per 10,000 patients and 7.98 (95%-CI 1.39 to 20.00; 14 studies) per 1 million treatments, for AE requiring treatment 1.14 (95%-CI 0.00 to 7.37; eight studies) per 1000 patients. Heterogeneity was substantial (I^2>80%). On average 9.4 AE occurred in 100 treatments of which half were bleeding, pain, or flare at the needle site argued to represent intended acupuncture reaction. AE definitions and assessments varied largely.

Conclusion

Acupuncture can be considered among the safer treatments in medicine. SAE are rare, and most common minor AE are very mild. AE requiring medical management are uncommon, but necessitate medical competence to assure patient safety. Clinical and methodological heterogeneity call for standardized AE assessments tools, clear criteria for differentiating acupuncture related AE from therapeutically desired reactions, and identification of patient related risk factors for AE.

PROSPERO registration number

CRD42020151930

Keywords

Adverse effects, adverse reactions, meta-analysis, safety, risk, pneumothorax

Strengths and limitations of this study

- First systematic review on acupuncture related adverse events including a risk of bias assessment
- First meta-analyses on adverse events related to acupuncture
- Complying with PRISMA guidelines
- Combining studies with heterogeneous AE definitions, but providing respective sensitivity analyses
- Causality assessment based on descriptions of adverse events as available from the included articles

Introduction

Acupuncture describes the insertion of fine needles at defined points on the patients' body for therapeutic or preventive purposes. It is used worldwide with growing popularity. In the EU acupuncture was identified as the most frequently provided method of complementary and alternative medicine (CAM) with 80,000 physicians and 16,380 non-medical practitioners.(1) In the UK alone 2.3 million traditional acupuncture treatments are carried each year.(2) In the US the number of acupuncturists doubled between 2002 and 2012.(3) The effectiveness of acupuncture is supported by level 1a evidence e.g. for chronic musculoskeletal pain and headache,(4-6) post-operative pain,(7, 8) post-operative nausea and vomiting,(9) as well as allergic rhinitis.(10) Furthermore, promising evidence exists for its potential role in the treatment of a large number of additional indications such as stroke rehabilitation,(11) depression,(12) aromatase inhibitor induced arthralgia,(13) and asthma.(14) Thus, acupuncture offers a non-pharmacological treatment option for various highly prevalent conditions with great disease burden and significant health economic impact. Long-term pharmacological treatment of these conditions is often associated with substantial side effects.(15, 16) Consequently, also risk estimates on acupuncture related adverse events (AE) are required for evidence-based risk benefit considerations that are essential for clinical decision making.

However, uncertainty remains about acupuncture safety. AE related to acupuncture are repeatedly and controversially discussed both in scientific literature as well as in public media. An overview of systematic reviews in 2017 (17) illustrates that many of the previous reviews on the safety of acupuncture just summarized case reports or case series. In turn, those reviews including studies that do allow for AE frequency estimation, such as cohort studies and large RCTs, mostly only addressed certain types of AE, particular patient groups, restricted acupuncture regimens, or certain countries. These data are surely important for clinical decision making in particular cases, but leave the overall risk of acupuncture related AE in the general population obscure. Additionally, debate exists about differentiating AE from therapeutically intended reactions that are claimed to form part of the acupuncture treatment. For example, international consensus exists that aggravation of symptoms represents an AE, since disease burden increases, although transient worsening of symptoms followed by long-term improvements can be interpreted as a so called healing crisis in complementary and alternative medicine.(18) In contrast, such consensus is still missing for local reactions such as small bleedings upon needle withdrawal, needling pain, and flare around the needling site. These are also referred to as beneficial signs by acupuncture experts and in standard text books and have been linked to neurophysiological mechanisms of acupuncture, suggesting that quality and intensity of these events should be considered when classifying them as AE.(19-21)

The last review on prospective studies on AE related to acupuncture with high external validity dates back to 2001,(22) did not meta-analytically summarize AE risk estimates and did not assess the quality of included studies. In addition, inconsistency and incompleteness of reporting in primary studies hampered the drawing of firm conclusions on acupuncture safety. Since then various large-scale clinical trials and nationwide surveys on acupuncture safety have been conducted.

Therefore, it was the aim of this review to provide an up to date summary of prospective trials that were particularly designed to evaluate AE related to needle acupuncture with manual or electrical stimulation in combination with or without moxibustion.

Methods

We systematically reviewed prospective studies that reported on acupuncture related AE. The protocol has been registered at the International prospective register of systematic reviews (PROSPERO) (23) on September 25, 2019 (registration number CRD42020151930; online supplementary appendix S1). The research checklist according to the

preferred reporting items for systematic reviews and meta-analyses (PRISMA) (24) is displayed in the online supplementary appendix S2.

Search strategy

We searched Pubmed, Scopus, and EMBASE for articles published before September 15, 2019 by applying the following search strategy: 1: acupuncture; 2: “adverse event”; 3:”adverse events”; 4: “adverse effect”; 5: “adverse effects”; #1 AND #2; #1 AND #3; #1 AND #4; #1 AND #5. Additional records were identified from previous reviews on acupuncture related AE.(17)

In- and exclusion criteria

We included articles reporting on prospective studies assessing AE associated with needle acupuncture involving manual or electrical stimulation combined with or without moxibustion in humans as their primary outcome. Only articles published in English or German were included. Publications on assessments of acupuncture point injection therapies or non-penetrating acupuncture point stimulation such as laser acupuncture, acupressure or transcutaneous electrical nerve stimulation (TENS) were excluded. We also excluded articles reporting solely on moxibustion or restricted acupuncture regimens such as press-needle, auricular or one-point acupuncture. Trials focusing just on one type of acupuncture related AE or just on a narrowly defined patient population were excluded.

Article selection and data extraction

Article selection was performed independently by two reviewers (WZ and PB, TS and PB, or LM and PB). Retrieved records were first screened for eligibility by abstract. Full texts were obtained for the remaining articles. Final decision about eligibility was obtained by consensus of all four reviewers.

Estimates of overall risks and risks for each reported type of AE were extracted as absolute number of patients with AE per total number of patients and treatments with AE per total number of treatments. Data concerning AE from sham- or placebo-acupuncture treatments were not extracted. The different types of AE were assigned to one of the following categories: bleeding, local pain, other local AE, distant pain, central nervous system, peripheral nervous system, vegetative nervous system, motor system, gastrointestinal / gynaecological system, cardiovascular system, respiratory system, generalized skin reactions, headache, emotional interference, sleeping problems, AE related to moxibustion, needling malpractice, aggravation of symptoms, other or unclassified AE (online supplementary appendix S3).

Following the differentiation between AE and adverse drug reactions (ADR) defined by the International Conference on Harmonization (ICH) of Good Clinical Practice,(25) articles were classified into reports on adverse events irrespective of their causal relationship to acupuncture and adverse reactions for which a causal relationship was a reasonable possibility. Serious adverse events (SAE) were reported as indicated in the included articles as in accordance with the ICH-criteria. These include any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.(25) Causality assessment of SAE was performed by independent acupuncture therapists who were medical doctors who received more than 300 hours of acupuncture training and with more than ten years of intensive acupuncture practice. As the basis of this assessment was limited to incomplete information provided in the articles lacking e.g. time references, categories of SAE causality were reduced to possibly or unlikely related to acupuncture or unclassifiable.

AE risk estimates given as patients with AE per total number of patients were interpreted according to the guidelines of the Council for International Organizations of Medical Sciences (CIOMS) as very common (≥ 1/10 patients), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000).(26)

Documentation of study characteristics included study type, country in which the study was conducted, reporter, method and time point of AE assessment, complaint as well as age and gender structure of the study population, average number and frequency of treatments per patient, average number of needles per treatment, needle in time, acupuncture style, and method of needle stimulation, as well as number, gender, training, and years of experience of acupuncturists. Data on patients' and acupuncturists' AE reports from the article published by Weidenhammer et al. in 2008 were handled as two separate trials.

Risk of bias assessment

Included studies were assessed for risk of bias according to a checklist developed by Faillie and colleagues for systematic reviews focusing on drug adverse events.(27) This checklist is applicable to RCTS, cohort studies, case-control studies, nested case-control studies, and systematic reviews. The questions are structured in 8 risk of bias domains. Possible answers are "Not applicable" (n/a), "Yes" (Y), "Unclear" (U), or "No" (N). A summary risk of bias assessment is provided for each domain as well as for the whole study. According to the inclusion criteria of this review, questions concerning systematic reviews, cross-over trials, and case-control studies were not applicable.

Data analysis

Data were analysed using the package meta implemented in R.(28) Pooled estimates with 95% confidence intervals (CI) for overall AE risk and risks of different types of AE were obtained from proportion meta-analyses. Random effects models were calculated by the Hartung-Knapp method with arcsine transformation of proportions. Cochran Q test, and I^2 statistics were used to assess the heterogeneity of included studies. Analysis were performed for the overall risks as well as the risks for the different types of AE given as the number of patients with AE per total number of patients undergoing an acupuncture series and as the number of treatments with AE per total number of treatments performed. AE that were reported separately in the articles, but that were allocated to the same AE category, were treated as they had occurred in different patients or treatments, respectively. Sensitivity analyses were performed for studies that explicitly only reported about AE that had, at the discretion of the assessors', a causal relationship to acupuncture treatments.

None of the articles reported the mean and variance of the number of AE per treatment. Thus, the expected number of AE per treatment could not be estimated by meta-analysis but just by considering the sum of AE relative to the sum of treatments. An additional sensitivity analysis was performed by excluding AE that are usually very mild and transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point. AE of such type that were indicated by any means as significant were not excluded for this sensitivity analysis.

Patient and public involvement

No patients were involved in defining the research question, the outcome measures, the design or conduct of this review. No patients were asked to advise on interpretation of results. Authors will share the results during patient seminars and information events. A concise version of the results will be made available for non-profit acupuncture organisations to be presented on their webpages.

Results

Study characteristics

7677 records were retrieved from the database search and two were identified from previous reviews on acupuncture related adverse events. 7499 records could be screened by abstract and for 180 articles full-texts were obtained. A total of 22 articles reporting on 21 studies covering 12.9 million treatments met our inclusion criteria (Figure 1).(29-50) In two studies different data assessments on different subpopulations were performed and are treated independently in the present analyses. In one study patient reported AE were assessed after one of the first treatments and three months after treatment,(36, 37) and in one large study AE were documented by therapists and in addition by a subgroup of patients.(44)

Study characteristics are provided in table 1. The four largest trials with one to five hundred thousand patients treated in over 750 thousand acupuncture sessions were cohort studies performed as part of the German Model Projects on Acupuncture (*Modellvorhaben Akupunktur*).(31, 39, 44, 47) Three nationwide surveys from the UK (described in four articles),(36-38, 46) one in-house surveillance report from Japan (49) and one summary of AE assessments nested within three Chinese RCTs (50) included two to six thousand patients receiving over 30 thousand treatments, respectively. In three surveys, two from South-Korea,(42, 43) one from Japan, (33) and one from Brazil,(30) around one to two thousand patients were included and treated in up to 14 thousand acupuncture sessions. One nationwide survey conducted in Sweden reported on the risk of AE based on data from over nine thousand acupuncture sessions.(41) In seven studies less than 500 patients receiving maximum 3.5 thousand treatments were included; four AE assessments nested within RCTS or clinical trials from China,(34, 45) Hong-Kong,(29) and Sweden,(35) one Japanese (48) and one German survey (32) as well as one German cohort study.(40) In most studies acupuncture was used to treat pain in middle aged patients. In six articles no details on the patients' condition were provided.(32, 33, 38, 41, 46, 48) Two articles reported explicitly on short-term AE after one particular treatment only.(37, 43) All but five articles provided sufficient information to infer that acupuncturists had a firm medical background and / or had received intensive acupuncture training.(32, 34, 35, 40, 41) One German survey also included "other practitioners" most likely non-medical practitioners (*Heilpraktiker*) with non-standardized acupuncture training.(32)

Eight articles described AE reported by patients only (29, 30, 35-37, 43, 44, 47) and seven articles AE reported by acupuncturists only.(31, 38, 39, 42, 44, 46, 49) As before said Weidenhammer et al. described therapists' and patients' reports on AE separately.(44) Zhao et al. combined the AE reports from patients and acupuncturists.(50) In five articles it was explicitly stated that acupuncturists recording the AE also queried their patients about any uncomfortable experience during or after treatment.(32-34, 41, 48) In two trials AE were documented by an independent assessor.(40, 45) In eight of the 22 included articles AE were reported irrespective of their relationship to acupuncture,(29, 31, 32, 35, 38, 46, 49, 50) while descriptions of AE assessments in twelve articles suggest that only AE related to the acupuncture treatment were documented,(30, 33, 34, 36, 37, 40-42, 44, 47, 48) and one article did not provide information about the AE definition.(43) Further discrepancies were found in definitions of certain reactions as therapeutically intended. For example, da Silva et al. did not count aggravation of symptoms as AE, because of difficulties in determining causality as well as severity and because of common notion among practitioners that transient worsening forms part of the acupuncture treatment.(30) In contrast White et al. reported observations of aggravated symptoms as AE, but only those that were not followed by substantial improvements.(46) In contrast, the other articles did not specify aggravation of symptoms further.(31-33, 35, 36, 40, 44, 47, 48) In addition, Endres et al. did report on erythema at the needling site (which was accounted for in the present analysis), but did not include it in their overall AE incidence report, as this can also be regarded as desired acupuncture reaction.(31)

1st Author year	Country	Study type	Patients			Treatments				Acupuncturists				AE assessment		
			n total (female)	Age [a]	Indication	n (total)	n / patient	n needles	Stimulation	n total (n female)	Medical background	Acupuncture training	Acupuncture practice	Reporter	Tool	Time point
Chung 2015	Hong-Kong	RCT	59 (46)*)	49 ± 10*)	Insomnia in major depressive disorder	531	9 / 3 w	14	EA	n.i.	TCM doctors	n.i.	> 3 a	P	SL & OQ any AE	after 3rd, 6th, 9th treatment
da Silva 2014	Brazil	Cohort monocentric	1157 (n.i.)	n.i.	Musculoskeletal, emotional &respiratory disorders i.a.	13,884	12#)	n.i.	MA	n.i.	MD	in training	n.i.	P	SL & OQ AE related to acu.	after each treatment
Endres 2004	Germany	Cohort nationwide private clinics	190,924 (130,974)	f: 58 ± 16 m: 55 ± 15	Chronic headache, LBP or arthrosis (> 6 m)	1.77 M	apx. 10 / 4 - 8 w	n.i.	n.i.	12,000 (n.i.)	MD	> 140 h	n.i.	A	SL & OQ any AE	after last treatment
Ernst 2003	Germany	Survey private practices	409 (279)	n.i.	n.i.	3,535	f: 9.0 m: 7.9	n.i.	n.i.	29 (n.i.)	MD & other practitioners	n.i.	n.i.	A also asking P	SL & OQ any AE	after each treatment; at subsequent visit
Furuse 2017	Japan	Survey 8 acupuncture clinics	2180 (1288)	54 ± 19	n.i.	14,039	6.4#	n.i.	MA, EA & Moxa	232 (93)	Japanese lic. acupuncturists	> 3 a	9 ± 10 a	A also asking P	SL AE related to acu.	after each treatment; at subsequent visit
Leung 2009	Hong-Kong	11 clinical trials (not specified)	254 (n.i.)	n.i.	Chronic pain, neurological & urological conditions	2,000	n.i.	5 avg.	MA & EA	2 (n.i.)	TCM doctors	n.i.	n.i.	A also asking P	SL AE related to acu.	after each treatment & subsequent visit
List 1992	Sweden	RCT monocentric	29 (n.i.)	median 40**)	Craniomandibular disorder	apx. 174	≥ 6 / 6 - 8 w	12 avg.	MA & EA	1 (0)	n.i.	n.i.	n.i.	P	SL & OQ any AE	after last treatment
MacPherson 2001	UK	Survey nationwide private practices	n.i.	n.i.	n.i.	34,407	n.i.	1 - 20	n.i.	574 (374)	MD & physio-therapists	1 – 2 a 11% ≥ 3 a 89%	< 10 a apx. 60% ≥ 10 a apx. 40%	A	SL & OQ any AE	upon recognition
MacPherson 2004 A	UK	Survey nationwide private practices	6,348 (4,821)	52 ± 15	Musculoskeletal, psychological, general, neurological, gyne-cological, obstetric & respiratory conditions; wellbeing	30,196	4.8	n.i.	MA & EA	638 (406)	MD & physio-therapists	> 3 a	< 10 a 58% ≥ 10 a 42%	P	SL & OQ AE related to acu.	3 m after inclusion
MacPherson 2005 A			9,408 (6,961)	51		9,408	1								SL imm. AE AE related to acu.	After the 1st / one of the 1st treatments
Melchart 1998	Germany	Cohort monocentric	121 (88)	54 ± 13	Mainly chronic pain	apx. 1,200	9.9 ± 4.7	n.i.	n.i.	n.i.	TCM doctors	n.i.	n.i.	Independent A asking P	SL & FT AE related to acu.	at subsequent visit
Melchart 2004	Germany	Cohort nationwide private clinics	97,733 (78,675)	55 ± 16	Chronic headache, osteoarthritis, LBP	apx. 760,000	7.8 ± 2.4	12.6 ± 5.1	n.i.	7050 (n.i.)	MD	> 140 h (19% > 350 h)	n.i.	A	SL & FT AE related to acu.	after last treatment
Odsberg 2001	Sweden	Survey private practices	n.i.	n.i.	n.i.	9,277	n.i.	n.i.	MA & EA	187 (n.i.)	Physio-therapists	n.i.	n.i.	A also asking P	n.i. AE related to acu.	after each treatment
Park 2009	South-Korea	Survey two-centred	1,095 (696)	58 ± 13	Stroke, headache, hyper-tension, dizziness, i.a.	1,095	1	n.i.	n.i.	8 (n.i.)	Korean medicine	n.i.	>10a	P	n.i.	after 1 arbitrary treatment
Park 2010	South-Korea	Survey private practices	2,226 (n.i.)	n.i.	n.i. (patients with AE mainly pain conditions)	3,071	1.4 / ≤ 5 w#)	n.i.	n.i.	13 (n.i.)	Oriental medicine.	6 a	< 3a 70% ≥ 3a 30%	A	SL AE related to acu.	upon recognition
Weiden-hammer 2008 B	Germany	Cohort nationwide private clinics	503,397 (40,5235)	54 ± 16	Chronic headache, LBP, osteoarthrosis (> 6 m)	4.2 M	8.4 (2.9)	n.i.	n.i.	9918 (3570)	MD	140 h (22% > 350 h)	n.i.	A	SL & FT AE related to acu.	after last treatment
			882847 (n.i.)	n.i.		7.9 M	n.i.								OQ - SAE only AE related to acu.	upon recognition
			5,998 (5,072)	55 ± 15		apx. 51582#)	8.6 (3.0)			9429 (n.i.)				P	OQ AE related to acu.	after last treatment
Wen 2016	China	RCT monocentric	120 (84)	59 ± 7	Posterior circulation ischemia	1,680	14 / 3 - 4 w	≤ 9	MA	1 (n.i.)	n.i.	n.i.	> 20 a	Blinded assessor	n.i. AE related to acu.	after each treatment
White 2001	UK	Survey private practices	n.i.	n.i.	n.i.	31,822	n.i.	n.i.	n.i.	78 (29)***)	MD & physio-therapists	≤ 100 h 43% > 100 h 57%	≤ 10 a 65% > 10 a 35%	A	SL & OQ any AE	upon recognition
Witt 2009	Germany	Cohort nationwide private clinics	229,230 (148,541)	51 ± 14	Chronic headache, osteo-arthritis, LBP, all. rhinitis, asthma, dysmenorrhea	2.2 M	10.2 ± 3.0	n.i.	n.i.	13579 (5418)	MD	> 140 h (15% > 350h)	6.9 ± 5.3 a	P	OQ AE related to acu.	after last treatment
Yamashita 1999	Japan	In-house surveillance	5,008 (2,804)	Mostly 40 - 50 a	Musculoskeletal disorder, miscellaneous complaints	65,482	13 avg.	n.i.	MA, EA & Moxa	84 (n.i.)	Japanese lic. acupuncturists	> 3 a	< 1 a 64% ≥ 1 a 36%	A	OQ any AE	upon recognition
Yamashita 2000	Japan	Survey monocentric	391 (n.i.)	12 - 88	n.i.	1,441	3.7#)	21#)	MA & EA	7 (n.i.)	Japanese lic. acupuncturists	> 3 a	n.i.	A also asking P	OQ AE related to acu.	after each treatment; at subsequent visit
Zhao 2011	China	3 RCTs multicenter	1,968 (1,239)	39 ± 14	Migraine, dyspepsia, Bell's palsy	39,360	20 / 4 w	2 - 5	MA & EA	n.i.	TCM doctors	≥ 8 a	> 10 a	P & A	SL & OQ any AE	after each treatment & after last treatment

Table 1: Study characteristics

AE: adverse event; SAE: serious adverse event; acu: acupuncture; MA: manual acupuncture; EA: electroacupuncture; Moxa: moxibustion; m: male, f: female; LBP: low back pain; MD: medical doctors; lic.: licensed; TCM: Traditional Chinese Medicine; SL: selection list; OQ: open questions, FT: free text; P: patients; A: acupuncturists; imm.: immediate; X ± X: mean ± standard deviation; a: year; w: weeks; h: hours; M: million; avg.: on average; i.a. inter alia; apx.: approximately; n.i.: not indicated; A) overlapping study populations from the same survey B) reports of patients and therapists separately presented; *) including one drop out prior to treatment; **) refers to total study population (n=61); ***) further professional details only provided by 59 acupuncturists; #) approximation based on other reported data

Overall risk of acupuncture related adverse events

Meta-analysis of 11 studies including 845,637 patients estimated the overall risk for at least one AE during a series of acupuncture treatments to be 9.31 (95%-CI 5.10 to 14.62) per 100 patients treated (Figure 2A). (29, 32, 34, 36, 39, 40, 44, 45, 47, 50) The median number of treatments per patient was 9 (min 4.8; max 14), and the total number of treatments exceeded 7.4 million. Visual inspection neither indicated an association of the incidence of AE with the number of treatments per acupuncture series nor with the study type (online supplementary appendix S4). Five studies reported the total number of acupuncture treatments with AE relative to the total number of treatments performed.(30, 32, 34, 38, 40) Meta-analysis of these studies covering 55,026 treatments in total resulted in a risk of 7.57 (95%-CI 1.43 to 17.95) treatments with AE per 100 treatments (Figure 2B). Sensitivity analysis of studies reporting on adverse acupuncture reactions and not on AE irrespective of their relationship to acupuncture treatments resulted in similar estimates (30, 34, 36, 38, 39, 44, 45, 47); 8.23 (95%-CI 6.42 to 10.25) patients with at least one AE out of 100 patients (Figure 2C) and 6.08 (95%-CI 0.00 to 38.76) treatment with AE out of 100 treatments (Figure 2D). Heterogeneity for all meta-analyses mentioned above (including the sensitivity analyses) was substantial as indicated by an I^2 between 98% and 100% ($p < 0.01$).

Thirteen articles reported the incidences of different types of AE per treatment (table 2).(30, 32-34, 37, 38, 40-43, 46, 48, 49) The average number of AE per 100 treatments varied between 0.14 and 69.12. In total 18,002 AE were reported in of 190,661 treatments, which makes on average 9.44 AE per 100 treatments. Exclusion of AE that are usually mild and transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point, reduced this number to 4.81 (min - max 0.10 – 36.92) AE per 100 treatments.

Study	Number of treatments	Number of AE		AE incidence per 100 treatments		Bleeding, pain, flare at needling site as % of all AE
		total	excluding bleeding, pain & flare	total	excluding bleeding, pain & flare	
Park 2009	1095	193	64	17.63	5.84	66.84%
Ernst 2003	3535	632	403	17.88	11.40	36.23%
Melchart 1998	1200	120	66	10.00	5.50	45.00%
Yamashita 1999	65482	94	67	0.14	0.10	28.72%
Yamashita 2000	1441	996	114	69.12	7.91	88.55%
MacPherson 2001	34407	4544	3406	13.21	9.90	25.04%
Odsberg 2001	9277	2108	390	22.72	4.20	81.50%
White 2001	31822	2176	820	6.84	2.58	62.32%
MacPherson 2005	9408	5071	3473	53.90	36.92	31.51%
Leung 2009	2000	8	0	0.40	0.00	100.00%
Park 2010	3071	99	26	3.22	0.85	73.74%
da Silva 2014	13884	1107	117	7.97	0.84	89.43%
Furuse 2017	14039	854	232	6.08	1.65	72.83%
Overall	190661	18002	9178	9.44	4.81	49.02%

Table 2: Number of adverse events (AE) per treatment

Serious acupuncture related adverse events

SAE were observed in five studies including 1,182,860 patients undergoing 10,570,678 treatments with incidences between two and 40 SAE in 100,000 patients undergoing a treatment series and between two and 99 in one million treatments, respectively.(31, 36, 39, 44, 49) Four articles reported that none of the AE observed in a total of 1,922 patients undergoing 19,005 treatments required medical treatment,(30, 34, 45, 48) and authors of five articles concluded that none of the AE observed in 122,699 treatments fulfilled the ICH-criteria for SAE.(33, 38, 42, 46, 50) Eight articles did not mention SAE or any AE description that allowed for inferences on SAE.(29, 32, 35, 37, 40, 41, 43, 47)

Meta-analyses of the overall risk for a SAE resulted in 1.01 (95%-CI 0.23 to 2.33) patients with SAE in 10,000 patients undergoing an acupuncture series (Figure 3A, 11 studies 1,188,930 patients) and 7.98 (95%-CI 1.39 to 20.00) SAE in one million treatments (Figure 3B, 14 studies 10,712,382 treatments). Exclusion of studies with zero SAE incidences changed these estimates to 1.47 (95%-CI 0.10 to 4.46) in 10,000 patients suffering from a SAE when undergoing an acupuncture series and 16.90 (95%-CI 0.49 to 56.60) in one million treatments causing an SAE. Sensitivity analyses of studies that only reported reactions with a plausible relationship to acupuncture resulted in risk estimates of 0.45 (95%-CI 0.06. to 1.18) SAE per 10,000 patients (Figure 3C) and 5.45 (95%-CI 0.50 to 15.67) per one million treatments (Figure 3D). Again, heterogeneity between studies included in these two meta-analyses was substantial ($I^2 > 85\%$, $p < 0.001$).

The causality assessment of the 73 SAE conducted by two acupuncture experts (table 3) resulted in 32 SAE (44%) being possibly related to acupuncture. Among those, pneumothorax, strong cardiovascular or vasovagal reactions, and fall or trauma were the most frequent SAE with a frequency of 1 to 3 cases in one million treatments each. One article that was not taken into account in the SAE meta-analyses as observed AE were not categorized in minor AE and SAE also reported two cases of pneumothorax in over 200,000 patients receiving on average 10 acupuncture treatments.(47) One of the included trials documented deaths occurring in the study population. Nineteen SAE (26%) were rate as unlikely related to acupuncture. Among those were nine deaths observed in one study in patients of an age between 67 and 87 years and related to a pre-existing health conditions.(31) Authors reported that the resulting death rate of 4.71 per 100,000 patients is below the expected death rate derived from population statistics. Other SAE classified as unlikely related to acupuncture were a circulatory reaction with amnesia, suicidal tendencies, acute general infection, a car crash two days after treatment, a malignant parotid tumour, tonic-clonic seizures, and an ophistotonus. Twenty-two SAE (30%), intervertebral disk prolapses and hospitalizations due to pain exacerbation or unknown reasons, were rated as “unclassifiable”.

Endres 2004	Causality	n
- Death	unlikely	9
- Fall or trauma, with or without fracture	possible	4
- Acute general infection with hospitalization	unlikely	2
- Allergic reaction to concomitant medication (atopy)	possible	1
- Stroke with hospitalization	unlikely	3
- Cardiovascular problems (hospital admission)	possible	3
- Intervertebral disk prolapse, pain exacerbation with hospital admission	unclassifiable	5
- Malignant parotid tumor (hospital admission)	unlikely	1
- Hospitalization (unknown reasons)	unclassifiable	17

Melchart 2004	Causality	n
- Exacerbation of depression	possible	1
- Hypertensive crisis	possible	1
- Vasovagal reaction	possible	1
- Asthma attack with hypertension and angina	possible	1
- Pneumothorax	possible	2

Yamashita 1999	Causality	n
- Hospitalization of patient with asthma because of coughing	possible	1
- 1 case of deep burn that recovered after 2 years	possible	1

Weidenhammer 2008 ther.	Causality	n
- Pneumothorax	possible	5
- Suicidiation in a patient with borderline syndrome	unlikely	1
- Hypertensive crisis	possible	1
- Syncope (vasovagal reaction)	possible	2
- Asthma attack in a patient with asthma	possible	1
- Erysipelas (one in a patient with lymphedema)	possible	2
- Circulatory collapse (one with uncontrolled defecation and one with vertigo and paresthesia)	possible	2
- Circulatory reaction with amnesia	unlikely	1
- Tonic-clonic seizures and ophistotonus	unlikely	1
- Infection of the knee joint with E. coli bacteria	possible	1

MacPherson 2004	Causality	n
- Low back pain in breast cancer patient, hospital admission, disappeared without medication, since then no more LBP	possible	1
- Car crash 2d after acupuncture, very little sleep the night before	unlikely	1
- Skin rash and feeling ill for several weeks accompanied by decrease of ME symptoms and feeling of catharsis (no treatment)	possible	1

Table 3: Causality assessment of serious adverse events as reported in included articles

The total number of serious adverse events (SAE) as well as the total number of treatments in each study can be identified from figure 3.

Acupuncture related adverse events requiring treatment

Meta-analysis combining eight studies including 1,211,791 patients yielded a summary estimate of 1.14 (95%-CI 0.00 to 7.37) in 1000 patients for the risk to suffer from an AE that required treatment when undergoing an acupuncture series (Figure 4). (29, 30, 34, 39, 44, 45, 47, 48) Also here, heterogeneity was substantial (I^2 100%). Two articles, that had defined required treatment as an SAE criterion, reported lower incidences (2 and 6 events per 100,000 patients) (39, 44) than other two articles, reporting on AE requiring treatment without referring to SAE (1.7 and 2.2 in 100 patients).(29, 47)

Risk of different types of minor adverse events

Overall risk for the different types of minor AE (categorization see online supplementary appendix S3) were estimated in separated meta-analyses as patients with AE per total number of patients undergoing a treatment series or as treatments with AE per total number of treatments (Table 4). Risks estimated in single studies (online supplementary appendix S5 and S6) varied largely for all types of minor AE. Most frequent and commonly occurring minor AE with summary risk estimated between one and five percent of patients undergoing an acupuncture series were bleeding events, pain at the needling site, other local AE, vegetative reactions, aggravation of symptoms, and events related to the central nervous system. Summary risk estimates for bleeding events, needle site pain, vegetative reactions, and aggravation of symptoms also ranged from 1% to 5% of treatments, while meta-analysis of symptoms related to the central nervous system per acupuncture treatment resulted in a risk of two in 1000 treatments. AE estimated to be uncommon with summary risk estimates of one to seven out of 1000 patients undergoing an acupuncture series were symptoms of the peripheral nervous system, pain distant to the needling site, gastrointestinal or gynaecological symptoms, headache, cardiovascular symptoms, affection of the motor system, generalized skin reactions, adverse emotional reactions, and sleeping problems. Symptoms affecting the peripheral nervous system, distant pain, as well as gastrointestinal or gynaecological symptoms were estimated to occur in one to seven out of 1000 treatments;

headache, cardiovascular, and motor symptoms as well as adverse emotional reactions only in one to eight out of 10,000 treatments. The risk for respiratory AE was estimated to be rare with a summary risk estimate of four out of 10,000 patients undergoing an acupuncture series and three out of 10,000 treatments. Summary risk estimates for AE caused by therapists' malpractice and burns caused by moxibustion were between one and two in 1000 patients undergoing an acupuncture series and between two in 10,000 to one in 1000 treatments, respectively.

Some of the studies showed outlying incidences for particular types of minor AE. List et al. observed at least one vegetative reaction in the course of an acupuncture series for craniomandibular disorder in over half of the patients (58.6%),(35) and MacPherson et al. reported vegetative reactions after over a quarter of treatments (27.9%).(37) These findings exceed the frequency of vegetative reactions of up to 13.6% of patients identified in the remaining studies and was mainly based on patient reports of abnormal tiredness after treatment. List et al. also report the highest incidence of aggravation of symptoms with 93% of CMD patients as well as the highest frequency of needle site pain with 44.8 % of patients. This was followed by an RCT with 32.2% of patients suffering needle site pain (29) and a cohort study among chronic pain patients of which 10% suffered aggravation of symptoms after receiving acupuncture.(40) The remaining 19 articles reported incidences smaller than 3% for aggravation of symptoms and 14% for needle site pain.

Type of AE	Number of studies	Sum of patients	Risk as patients with AE per 100 patients [95%-CI] overall	min	max	Tau² I²	Number of studies	Sum of treatments	Risk as treatments with AE per 100 treatments [95%-CI] overall	min	max	Tau² I²
Bleeding	13	1038741	4.67 [2.08; 8.22]	0.48 [0.32; 0.67]	25.18 [21.10; 29.50]	0.0008 99.4%**	13	190661	4.92 [1.18; 11.01]	0.03 [0.02; 0.05]	45.45 [42.89; 48.03]	0.0169 99.9%**
Needle site pain	14	1038907	3.75 [0.74; 8.94]	0.05 [0.04; 0.06]	44.83 [27.46; 62.87]	0.0085 99.9%**	12	188661	2.43 [0.63; 5.35]	0.01 [0.00; 0.02]	15.75 [13.92; 17.68]	0.0095 99.8%**
Other local AE	10	1034610	2.79 [0.02; 10.01]	0.15 [0.14; 0.16]	35.59 [23.97; 48.14]	0.0494 100.0%*	11	187566	0.13 [0.04; 0.27]	0.00 [0.00; 0.01]	0.90 [0.48; 1.46]	0.0004 96.4%**
Vegetative reaction	12	1036607	1.95 [0.40; 4.63]	0.08 [0.07; 0.08]	58.62 [40.52; 75.59]	0.0012 99.7%**	12	188661	2.24 [0.21; 6.35]	0.00 [0.00; 0.01]	27.87 [26.97; 28.78]	0.0213 99.9%**
Aggravation of symptoms	11	1036760	1.48 [0.00; 5.90]	0.08 [0.07; 0.09]	93.10 [81.26; 99.30]	0.0017 99.8%**	10	173682	0.84 [0.26; 1.75]	0.00 [0.00; 0.01]	2.83 [2.66; 3.01]	0.0055 99.7%**
Central nervous system	9	244553	1.45 [0.07; 4.51]	0.05 [0.00; 0.20]	37.93 [21.45; 55.99]	0.0018 96.3%**	11	179253	0.20 [0.05; 0.46]	0.01 [0.00; 0.02]	1.08 [0.76; 1.44]	0.0011 98.4%**
Peripheral nervous system	8	433118	0.69 [0.02; 2.34]	0.08 [0.07; 0.10]	27.59 [13.14; 44.96]	0.0004 98.1%**	10	152813	0.19 [0.02; 0.55]	0.00 [0.00; 0.01]	1.46 [0.84; 2.26]	0.0008 98.0%**
Distant pain	5	241817	0.60 [0.21; 1.20]	0.17 [0.09; 0.29]	0.95 [0.72; 1.21]	0.0005 92.6%**	4	46456	0.73 [0.00; 5.02]	0.07 [0.00; 0.27]	4.49 [4.08; 4.91]	0.0085 99.5%**
Gastrointestinal / gynaecologcial system	9	747559	0.60 [0.04; 1.81]	0.01 [0.01; 0.02]	17.24 [5.94; 32.83]	0.0008 99.3%**	10	186125	0.15 [0.03; 0.38]	0.01 [0.00; 0.02]	1.18 [0.97; 1.41]	0.0008 98.2%**
Unclassified AE	10	1036307	0.57 [0.01; 1.95]	0.07 [0.05; 0.08]	17.85 [14.29; 21.70]	0.0003 99.0%**	9	172136	0.47 [0.03; 1.46]	0.00 [0.00; 0.01]	5.46 [4.74; 6.23]	0.0025 99.4%**
Headache	9	845745	0.51 [0.03; 1.55]	0.03 [0.03; 0.04]	13.56 [6.10; 23.38]	0.0012 99.6%**	7	97592	0.04 [0.01; 0.10]	0.00 [0.00; 0.01]	0.14 [0.01; 0.40]	0.0002 90.3%**
Cardiovascular system	5	739155	0.40 [0.24; 0.61]	0.27 [0.25; 0.29]	0.83 [0.00; 3.21]	0.0001 96.4%**	3	18774	0.03 [0.00; 0.13]	0.01 [0.00; 0.04]	0.08 [0.00; 0.33]	0.0001 21.2%
Motor system	5	237634	0.38 [0.00; 4.79]	0.08 [0.07; 0.09]	41.38 [24.41; 59.48]	0.0011 94.6%**	5	82112	0.01 [0.00; 0.04]	0.00 [0.00; 0.01]	0.03 [0.00; 0.11]	0.0001 58.1%*
Generalized skin reaction	2	229289	0.35 [0.00; 35.67]	0.09 [0.08; 0.10]	1.69 [0.00; 6.52]	0.0029 58.2%	-					
Needling malpractice	7	1029871	0.22 [0.01; 0.67]	0.00 [0.00; 0.00]	1.04 [0.81; 1.30]	0.0009 99.7%**	7	164146	0.12 [0.02; 0.28]	0.01 [0.00; 0.02]	0.62 [0.28; 1.10]	0.0002 95.1%**
Emotional interference	6	930429	0.20 [0.00; 0.81]	0.02 [0.02; 0.02]	1.24 [0.99; 1.53]	0.0002 98.7%**	7	155131	0.08 [0.00; 0.27]	0.01 [0.00; 0.02]	0.67 [0.51; 0.84]	0.0004 96.8%**
Sleeping problems	5	432529	0.16 [0.00; 0.91]	0.04 [0.03; 0.05]	20.69 [8.19; 37.03]	0.0001 97.1%**	-					
AE caused by moxibustion	4	428682	0.14 [0.00; 1.16]	0.00 [0.00; 0.00]	0.96 [0.60; 1.42]	0.0002 98.3%**	4	145750	0.02 [0.00; 0.18]	0.00 [0.00; 0.01]	0.17 [0.11; 0.25]	0.0001 95.0%**
Respiratory system	3	235637	0.04 [0.00; 0.26]	0.02 [0.01; 0.02]	0.24 [0.00; 0.96]	0.0001 69.0%*	1	3535	0.03 [0.00; 0.11]			

Table 4: Summary risk estimated for different types of adverse events

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses; min: minimum; max: maximum; 95%-CI: 95% confidence interval *: p-value of Q-test for heterogeneity < 0.05; **: p-value of Q-test < 0.00

Risk of bias assessment

According to the inclusion criteria the study objective was clearly described in all articles (Figure 5, category A). Study design was clear for all but one article, which stated that data were collected in the course of 11 clinical trials without further specification.(34) Also, all but one AE assessment were free of a run in period. In one RCT the safety assessment was initiated with a short delay.(35) Both irregularities were rated as unlikely to introduce bias into AE documentation. High risk for selection bias (Figure 5, category B) was identified for the four RCTs and the AE assessment in 11 clinical trials (23% of articles), due to exclusion of patients with comorbidities or bleeding tendency. In contrast, in all surveys and cohort studies (77%) the risk for selection bias was rated as unclear due to an indistinct selection of therapists and / or patients, inclusion of voluntarily participating acupuncturists or acupuncturists from specialized medical centres only. Furthermore, none of the articles stated that patients were naive to acupuncture. Risk of bias due to study withdrawal or drop-out (Figure 5, category C) was rated as low for all RCTs and two surveys, that only reported on short-term AE (27%), (37, 43) and as high for one survey (5%), because treatment was ceased for 40% of patients with AE.(42) For the remaining studies (68%) the risk of bias due to early treatment termination was rated as unclear, as withdrawals and drop-outs due to AE were not reported. The risk of information bias regarding the safety outcome (Figure 5, category D) was rated as high for one study (5%) because of an exclusive documentation of repeatedly occurring AE (35) and as unclear for all remaining studies (95%). At this, AE reporting by patients or acupuncturists instead of an independent assessor was classified as an unclear risk for social desirability bias. Using only a selection list (33, 34, 37, 42) or only open questions as AE assessment tool,(47-49), lack of reporting on the AE assessment tool (41, 43, 45) or the definition of the safety outcome, and selection of the time-point of the AE assessment (only directly after treatment,(30, 31, 41, 45) only after the last treatment initiation,(35, 36, 39, 44, 47) solely upon recognition (38, 42, 46, 49)) were rated as possible but unclear sources of detection bias. Further risk of information bias (Figure 5, category E) appeared to be unclear due to poor reporting of treatment details in all but seven studies (32%).(29, 35, 38, 39, 45, 48, 50) Bias arising from differential care, confounder assessment and statistical methods to control for confounding (Figure 5, category F) was rated as low, as crude AE risk estimates and not relative risks with respect to a comparator group were extracted. The risk of bias due to other statistical methods (Figure 5, category G) was also rated as low, as reporting of AE incidence was clear and well-structured in all articles.

Bias due to conflict of interest (Figure 5, category H) might be present in four articles (18%) due to funding by institution with direct interest in the public acknowledgement of acupuncture.(36, 37, 41, 42) In eight articles (36%) funding or other conflicts of interest were not described.(32, 34, 35, 38, 40, 46, 48, 49) The ten remaining articles (45%) included an explicit statement about funding by independent institutions and absence of other conflicts of interest.

Discussion

Overall risk for acupuncture related adverse events

To date this is the first systematic review on prospective studies that provides summary risk estimates for acupuncture related adverse events derived from meta-analyses. The obtained results suggest that AE can be expected in every tenth patient that undergoes a series of acupuncture treatments and, overall, in every 13th treatment. Minor AE were common and represented the large majority of reported AE. About half of the reported minor AE are usually mild and transient or might even be regarded as part of the acupuncture treatment or therapeutically intended reactions (bleeding, needle site pain, flare around the needle site).(21) SAE can be expected rarely in about every 10,000th patient in the course of an acupuncture series and, overall, in every 125,000th treatment. Sensitivity analyses excluding studies with zero SAE incidences still suggest SAE being rare (every 7000th patient and every 60,000th treatment)

particularly in comparison to SAE risk associated with pharmacological treatments.(16, 51, 52) AE requiring treatment occur uncommonly in about every 900th treatment, but additional AE are likely to also have involved medical decision-making about further diagnostics and follow-up. With meta-analyses for the overall risk of acupuncture related AE covering over 845,637 patients undergoing more than 7.4 million treatments and for the risk of SAE covering more than 1.2 million patients and 10.6 million treatments, the amount of data is equivalent to such available on the safety of e.g. common analgesics.(53, 54) This work augments insights on acupuncture related adverse events from previous reviews with either narrow eligibility criteria or focussing on case reports.(17) It includes data from the largest and most rigorous trials on acupuncture safety e.g. from the large nationwide cohort studies conducted in the UK and Germany which had not yet been aggregated.(31, 36-39, 44, 46, 47) Thus, our results provide rigorous support for the previously drawn conclusion (22, 55, 56) that acupuncture is among the safe treatments in medicine with SAE occurring rarely and half of the common minor AE being mild and transient. The uncommon AE requiring treatment necessitate solid medical competence of acupuncturists.

Types of adverse events related to acupuncture and implications for medical education of acupuncturists

Common minor AE were bleeding, needle site pain, other local reactions at the needling site, vegetative reactions, aggravation of symptoms, and AE related to the central nervous system (one to five out of 100 patients). This is in line with other reviews (22, 57) also on auricular (58) and paediatric acupuncture.(56) All other types of minor AE can be regarded as uncommon (1 to 7 out of 1000 patients), despite respiratory reactions that occurred very rarely (4 out of 10,000 patients). SAE most often reported were pneumothorax, strong cardiovascular or vasovagal reactions, and fall or trauma with one to three cases in one million treatments. Several other sometimes fatal SAE repeatedly described in case reports were not observed in the included studies; e.g. traumatic injuries of inner organs, local and systemic infections, subarachnoid bleeding, infective endocarditis, and cardiac tamponade.(59-63) This is likely due to the fact that acupuncturists in most of the studies were well trained, as SAE are claimed to be avoidable by proper acupuncture training and practice. Concordantly, cases of acupuncture malpractice were uncommon in the included trials.

Heterogeneity between studies

Possible causes of the substantial heterogeneity observed in all meta-analyses are differences in patient populations, needling regimens, AE definition, and AE assessment. Sensitivity analyses of trials reporting on adverse reactions with a plausible relationship to acupuncture resulted in only marginally lower overall AE risk estimates, but in a 50% lower SAE risk per patient and a 30% lower SAE risk per treatment. Reporting of SAE irrespective of the relationship to acupuncture is surely more conservative but likely to cause risk overestimation. In line with this, the causality of more than half of the SAE was rated as unlikely or unclassifiable by two independent acupuncture experts.

The variety of combinations of further patient treatment and assessment related factors prevented meaningful subgrouping of studies for additional sensitivity analyses, and the likeliness of their contribution to the observed heterogeneity makes formal assessment for publication bias unadvisable.(64) However, some distinct observations are worth to be discussed. Certain patient populations might be at higher risk to experience acupuncture related AE; e.g. in one study conducted among CMD patients AE were prominently frequent.(35) The role of acupuncture regimens in explaining heterogeneity could not be determined due to the limited information about number, location, and stimulation of needles. In contrast, the number of treatments per acupuncture series and study type seemed not to have impacted reported AE incidences.

A further possible cause of heterogeneity are differences in contrasting AE from therapeutically intended reactions that form part of acupuncture treatment; e.g. in contrast to international consensus, (18) aggravated symptoms were not or only in part counted as AE in two studies. (30, 46) Local reactions such as bleeding, pain, and flare at the needling

site that represented half of the AE reported and are referred to as beneficial signs in standard acupuncture textbooks and by authors themselves.(20, 31) As the principle of acupuncture is to induce endogenous anti-nociceptive mechanisms and anti-inflammatory humoral responses through micro-trauma of skin and tissue, it can be argued that moderate local reactions are indeed desired reactions indicating an induction of regulative processes. Mild pain and a flare at the needling site have been linked to important neurophysiological mechanisms of acupuncture.(21) Additionally, aching or soreness at the needling site might be part of the intended deqi sensation (propagated sensation along the channels) supposedly related to acupuncture effectiveness.(19) The loss of small drops of blood upon needle withdrawal is interpreted as a sign for the patient's constitution called "excess" or "excess heat" in TCM terminology and was suggested not to be interpreted as AE.(65) On the other hand, standard text books explicitly explain needling techniques avoiding pain and bleeding.(20, 66) This debate calls for a uniform internationally recognized consensus on the definition of local acupuncture reactions as AE e.g. according to their quality and intensity.

In addition, included studies differed in reporters (acupuncturists, patients, acupuncturists also questioning patients, and independent assessors), the type of documentation (selection list, open questions, or a combination of both), and assessment time points. Due to the large variability of combinations the individual impact of these factors could not be estimated, but literature suggests that patients report more AE than therapists,(67) and that open questions presented to patients lead to lower risk estimates than the presentation of a selection list of possible AE.(29) Thus, standardized AE assessment methods should be established for acupuncture studies.

Risk of bias in included studies

Although, large prospective studies are among the most important sources of safety data, they come with the known risk for information, selection, and confounding bias.(68) Risk of information bias was mostly related to poor reporting of acupuncture regimens and the discrepancies in AE definition and assessment. This is in line with the shortcoming identified for reporting of AE in acupuncture randomized controlled trials.(69) Possible causes of selection bias identified were mainly voluntary participation of practitioners, unsystematic patient selection, and study conductance in highly specialized institutions. Practical reasons make these causes of selection bias inherent to safety studies. They, however, are unlikely to importantly impair external validity, considering the large number of patients and treatments, the variety of countries in which studies were conducted, and the inclusion of different study designs. Future large scale comparative safety studies along with modern statistical methods for confounder adjustment could be used to contrast AE risks related acupuncture to AE risks associated with other treatments and to identify patient and treatment characteristics associated with AE in real world clinical settings.(70)

Limitations

First, it is debatable whether studies should be summarized irrespective of whether AE not necessarily related to acupuncture or adverse reactions likely caused by acupuncture were reported. In order to provide the most comprehensive information possible respective sensitivity analyses were conducted. Additionally, the risk estimates for the different types of minor adverse events are likely to be slightly overestimated and should be interpreted as a rough indication that allows to distinguish frequent from less frequent acupuncture related minor AE. In categorizing the minor AE it was disregarded that several different AE falling in one category could have occurred in the same patient or during the same treatment. Also, calculations of risks in treatments with AE per total number of treatments could not adjust for the fact that multiple AE assessments in the same patient are not independent. Furthermore, zero incidences of certain types of AE were not available. Finally, the causality assessment presented for SAE is limited to

expert opinions and is only based on the information provided in the respective article. Such an evaluation does not replace a rigorous causality assessment that would involve querying patients and therapists.

Clinical implications

Patients should be informed that acupuncture commonly causes minor AE, but rarely SAE. Examples for SAE should at least cover the most frequent ones, pneumothorax and strong cardiovascular or vasovagal reactions potentially leading to fall or trauma, along with the respective incidence of 1-3 per million treatments. Patients should also be made aware of the fact that great part of the minor AE are either very mild or even intended effects that indicate a beneficial physiological reactions. However, they should be encouraged to report any prolonged discomfort or pain that are to be avoided during treatment. Acupuncturists should carefully balance treatment intensity according to patients' reactions in order to minimize AE. They should assess local AE upon needle withdrawal and query patients about AE directly after treatment as well as at the subsequent visit. Therapists should be aware that, although uncommon, AE requiring treatment can be expected and necessitate medical decision making. Medical competence is also required for the indication of acupuncture in patients at high risk for AE or those in which AE could lead to particular aversive outcomes such as pregnant women, elderly and patients with cardiovascular comorbidities. In these patients acupuncture can be especially beneficial, as conventional treatments e.g. with analgesics are often limited by side effects or drug interactions, but selection of acupuncture regimens needs to involve careful risk-benefit considerations. Theses medical competences required to provide optimal patient safety should also be reflected by acupuncture education standards and regulations. At this policy makers should take into account the worldwide popularity of acupuncture which is likely to further increase as its scientific level of evidence has led to more than 4000 practice guidelines recommending acupuncture for different mostly pain indications.(69)

Conclusion

Acupuncture can be considered among the safer treatments in medicine. It rarely causes SAE and the majority of the common minor AE are very mild. AE requiring medical management are uncommon. For optimal patient safety acupuncture education standards regulations should reflect that solid medical competence of acupuncturists is required to manage AE properly and to minimize the risk of malpractice. Clinical and methodological heterogeneity calls for an international consensus on AE assessment tools in acupuncture studies and criteria for differentiating acupuncture related AE from therapeutically desired reactions as well as identification of patient related risk factors for acupuncture related AE. In particular, comparative safety studies are needed to contrast acupuncture to standard care in its main indications.

Figure legends

Figure 1: Flow diagram

Designed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)(24)

Figure 2: Meta-analyses of the overall risk for acupuncture related adverse events

Summary risk estimates for adverse events (AE) were calculated as the number of patients or treatments with at least one AE relative to the total number of patients or treatments, respectively.

Figure 3: Meta-analyses of the overall risk for serious adverse events related to acupuncture

Summary risk estimates for serious adverse events (SAE) were calculated as the number SAE cases relative to the total number of patients or treatments, respectively.

Figure 4: Meta-analyses of the overall risk for adverse events (AE) requiring treatment

Summary risk estimates for AE requiring treatment were calculated as the number of patients with such AE relative to the total number of patients.

Figure 5: Risk of bias assessment

Risk of bias assessment was conducted according to Faillie et al.(27) L – green: low risk of bias, U – yellow: unclear risk of bias, H – red: high risk of bias

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. DI reports to recieve honorarium and travel costs from non-profit academic organizations, physician chambers and universities for teaching and lecturing and to serve as president of the German Medical Acupuncture Association (Deutsche Ärztegesellschaft für Akupunktur, DÄGfA, a non-profit medical associations). PB declares to recieve honorarium and travel costs from non-profit academic organizations and universities for teaching and lecturing and to be member of the scientific advisory board of the DÄGfA. WZ and TS declare: no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

DI, PB and WZ defined the research question as well as in and exclusion criteria for this systematic review. WZ, TS and PB were responsible for article screening, data extraction and classifications of adverse events. TS and PB performed the quality assessment. Questions and discrepancies were discussed among all authors until consent was achieved. PB conducted the meta-analyses and designed table and figures. All authors contributed to drafting the manuscript and approved its final version for publication.

The corresponding author (PB) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. As the senior author, DI is the guarantor of the work presented in this manuscript. DI accepts full responsibility for the finished article, has access to any data and controlled the decision to publish

Transparency declaration

The lead author DI affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that the review and analyses were conducted as planned.

Ethical approval

Not required.

Data sharing

The full set of extracted data and the R-code underlying the meta-analyses are available from the corresponding and senior author (Petra.Baeumler@med.uni-muenchen.de, Dominik.Irnich@med.uni-muenchen.de).

Dissemination to participants and related patient and public communities

Authors plan to disseminate the findings of this review to patients, clinicians, policy makers and the general public through various channels including newsletters, newspapers and magazines. In special regard to patient information, results will be shared during patient seminars and information events, and a concise version of the results will be made available for non-profit acupuncture organisations to be presented on their webpages.

Trial registration

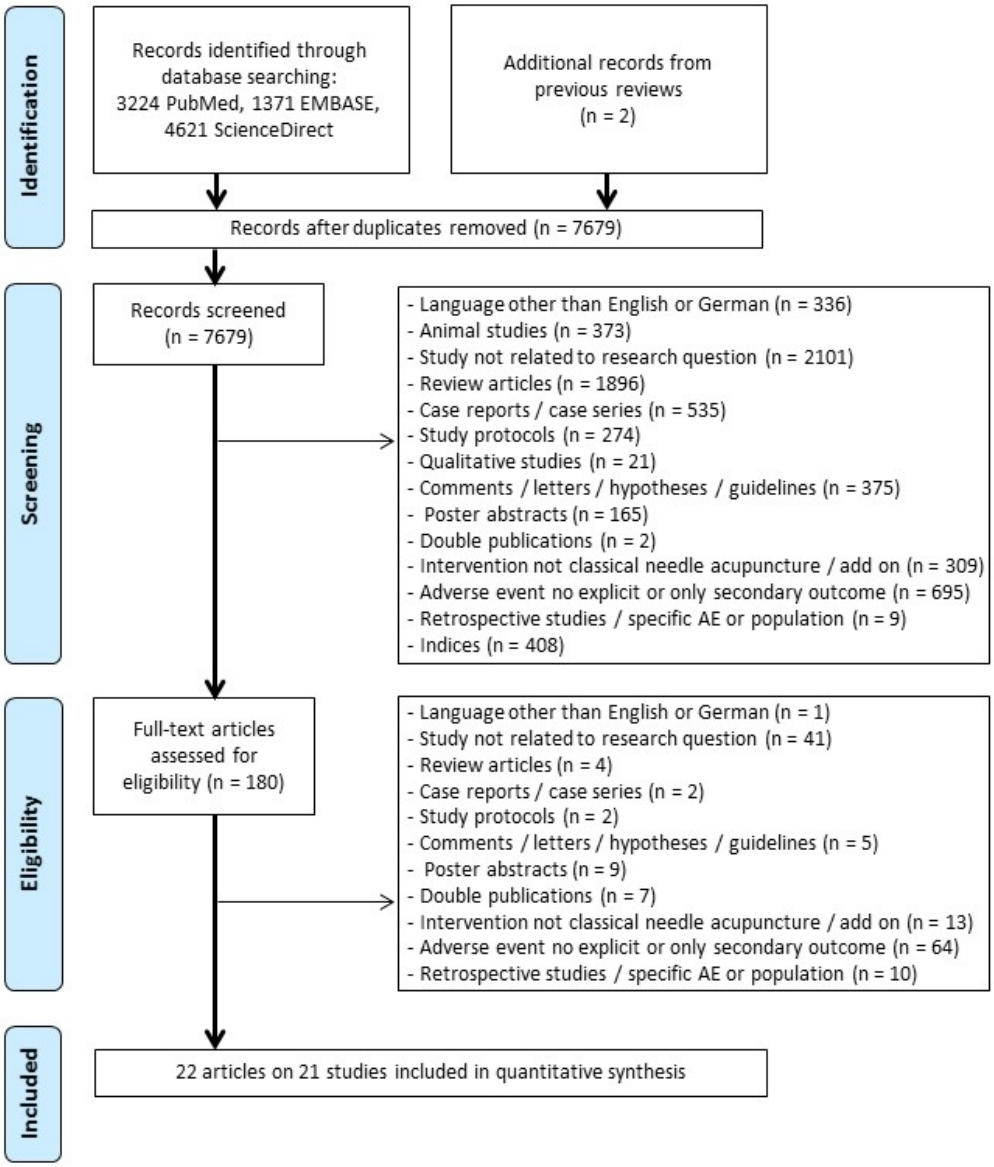
PROSPERO registration number CRD42020151930. To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. It has not been checked for eligibility or for sense by the PROSPERO team.

References

1. Ammon K, Cardini F, Daig U, Dragan S, Frei-Erb M, Hegyi G, et al. Final Report of CAMbrella Work Package 5 - Helath Technology Assessment (HTA) and a map of CAM provision in the EU [Internet]. CAMbrella - A pan-European research network for Complementary and Alternative Medicine (CAM); 2013 [updated 17.09.2013]. 14]. Available from: https://phaidra.univie.ac.at/view/o:300096.
2. British Acupuncture Council. Acupuncture practitioners in the UK [Internet]. 2016 [updated 2016]. Available from: https://www.acupuncture.org.uk/public-content/about-the-bacc/4115-acupuncture-practitioners-in-the-uk.html.
3. Cui J, Wang S, Ren J, Zhang J, Jing J. Use of acupuncture in the USA: changes over a decade (2002-2012). Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2017;35(3):200-7.
4. Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. J Pain. 2018;19(5):455-74.
5. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev. 2016(6):Cd001218.
6. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Shin BC, et al. Acupuncture for the prevention of tension-type headache. Cochrane Database Syst Rev. 2016;4:Cd007587.
7. Tedesco D, Gori D, Desai KR, Asch S, Carroll IR, Curtin C, et al. Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty: A Systematic Review and Meta-analysis. JAMA surgery. 2017;152(10):e172872.
8. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British journal of anaesthesia. 2008;101(2):151-60.
9. Lee A, Chan SK, Fan LT. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2015(11):Cd003281.
10. Feng S, Han M, Fan Y, Yang G, Liao Z, Liao W, et al. Acupuncture for the treatment of allergic rhinitis: a systematic review and meta-analysis. American journal of rhinology & allergy. 2015;29(1):57-62.
11. Yang A, Wu HM, Tang JL, Xu L, Yang M, Liu GJ. Acupuncture for stroke rehabilitation. Cochrane Database Syst Rev. 2016(8):Cd004131.
12. Smith CA, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. Cochrane Database Syst Rev. 2018;3:Cd004046.
13. Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA. 2018;320(2):167-76.
14. Brinkhaus B, Roll S, Jena S, Icke K, Adam D, Binting S, et al. Acupuncture in Patients with Allergic Asthma: A Randomized Pragmatic Trial. J Altern Complem Med. 2017;23(4):268-77.
15. Whiskey E, Taylor D. A review of the adverse effects and safety of noradrenergic antidepressants. Journal of psychopharmacology (Oxford, England). 2013;27(8):732-9.
16. Carter GT, Duong V, Ho S, Ngo KC, Greer CL, Weeks DL. Side effects of commonly prescribed analgesic medications. Physical medicine and rehabilitation clinics of North America. 2014;25(2):457-70.
17. Chan MWC, Wu XY, Wu JCY, Wong SYS, Chung VCH. Safety of Acupuncture: Overview of Systematic Reviews. Sci Rep. 2017;7(1):3369.
18. White A, Boon H, Alraek T, Lewith G, Liu JP, Norheim AJ, et al. Reducing the risk of complementary and alternative medicine (CAM):Challenges and priorities. Eur J Integr Med. 2014;6(4):404-8.
19. Ren YL, Guo TP, Du HB, Zheng HB, Ma TT, Fang L, et al. A survey of the practice and perspectives of chinese acupuncturists on deqi. Evidence-based complementary and alternative medicine : eCAM. 2015;2015:684708.
20. Shanghai College of Traditional Medicine. Acupuncture - a comprehensive text. Seattle, USA: Eastland Press; 1981.
21. Zhu H. Acupoints Initiate the Healing Process. Medical acupuncture. 2014;26(5):264-70.
22. Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. Am J Med. 2001;110(6):481-5.
23. University of York Y, UK. International prospective register of systematic reviews (PROSPERO) [Internet]. [Available from: https://www.crd.york.ac.uk/prospero.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

25. European Medicines Agency. Guideline for good clinical practice E6(R2) [Internet]. 2016 [updated 2016]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.
26. Council for International organizations of medical sciences - CIOMS. Guidelines for Preparing Core Clinical-Safety Information on Drugs Second Edition – Report of CIOMS Working Groups III and V [Internet]. 1999 [updated 1999]. Available from: https://cioms.ch/shop/product/guidelines-preparing-core-clinical-safety-information-drugs-second-edition-report-cioms-working-groups-iii-v/.
27. Faillie JL, Ferrer P, Gouverneur A, Driot D, Berkemeyer S, Vidal X, et al. A new risk of bias checklist applicable to randomized trials, observational studies, and systematic reviews was developed and validated to be used for systematic reviews focusing on drug adverse events. J Clin Epidemiol. 2017;86:168-75.
28. Schwarzer G. meta: {A}n {R} package for meta-analysis. R News. 2007;7(3):40-5.
29. Chung KF, Yeung WF, Yu YM, Kwok CW, Zhang SP, Zhang ZJ. Adverse Events Related to Acupuncture: Development and Testing of a Rating Scale. Clin J Pain. 2015;31(10):922-8.
30. da Silva JBG, Saidah R, Megid CBC, Ramos NA. Adverse events following acupuncture: A prospective survey of 13,884 consultations in a university out-patient acupuncture training clinic in Brazil. Eur J Integr Med. 2014;6(4):488-91.
31. Endres HG, Molsberger A, Lungenhausen M, Trampisch HJ. An internal standard for verifying the accuracy of serious adverse event reporting: the example of an acupuncture study of 190,924 patients. Eur J Med Res. 2004;9(12):545-51.
32. Ernst G, Strzyz H, Hagmeister H. Incidence of adverse effects during acupuncture therapy—a multicentre survey. Complementary therapies in medicine. 2003;11(2):93-7.
33. Furuse N, Shinbara H, Uehara A, Sugawara M, Yamazaki T, Hosaka M, et al. A Multicenter Prospective Survey of Adverse Events Associated with Acupuncture and Moxibustion in Japan. Medical acupuncture. 2017;29(3):155-62.
34. Leung PC, Zhang L, Cheng KF. Acupuncture: Complications are preventable not adverse events. Chin J Integr Med. 2009;15(3):229-32.
35. List T, Helkimo M. Adverse events of acupuncture and occlusal splint therapy in the treatment of craniomandibular disorders. CRANIO. 1992;10(4):318-26.
36. MacPherson H, Scullion A, Thomas KJ, Walters S. Patient reports of adverse events associated with acupuncture treatment: A prospective national survey. Qual Saf Health Care. 2004;13(5):349-55.
37. MacPherson H, Thomas K. Short term reactions to acupuncture--a cross-sectional survey of patient reports. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2005;23(3):112-20.
38. MacPherson H, Thomas K, Walters S, Fitter M. A prospective of adverse events and treatment reactions following 34,000 consultations with professional acupuncturist. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2001;19(2):93-102.
39. Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, et al. Prospective Investigation of Adverse Effects of Acupuncture in 97 733 Patients. Arch Intern Med. 2004;164(1):104-5.
40. Melchart DV, Hager S, Weidenhammer W, Liao JZ, Liu Y, Linde K. Adverse effects and concomitant symptoms associated with acupuncture treatment - A pilot study. Akupunktur. 1998;26(2):87-92.
41. Odsberg A, Schill U, Haker E. Acupuncture treatment: side effects and complications reported by Swedish physiotherapists. Complementary therapies in medicine. 2001;9(1):17-20.
42. Park JE, Lee MS, Choi JY, Kim BY, Choi SM. Adverse events associated with acupuncture: A prospective survey. J Altern Complem Med. 2010;16(9):959-63.
43. Park SU, Ko CN, Bae HS, Jung WS, Moon SK, Cho KH, et al. Short-term reactions to acupuncture treatment and adverse events following acupuncture: A cross-sectional survey of patient reports in Korea. J Altern Complem Med. 2009;15(12):1275-83.
44. Weidenhammer W, Streng A, Melchart D, Linde K. Unerwünschte Wirkungen und Komplikationen bei Akupunkturbehandlung: Ergebnisse der großen Beobachtungsstudie im Rahmen des Modellvorhabens der Ersatzkassen. Dtsch Zeitschrift für Akupunkt. 2008;51(3):6-14.
45. Wen Y, Zhang C, Zhao XF, Deng SZ, He S, Huang LH, et al. Safety of different acupuncture manipulations for posterior circulation ischemia with vertigo. Neural Regen Res. 2016;11(8):1267-73.
46. White A, Hayhoe S, Hart A, Ernst E. Survey of adverse events following acupuncture (SAFA): A prospective study of 32,000 consultations. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2001;19(2):84-92.

47. Witt CM, Pach D, Brinkhaus B, Wruck K, Tag B, Mank S, et al. Safety of acupuncture: Results of a prospective observational study with 229,230 patients and introduction of a medical information and consent form. Forsch Komplementmed. 2009;16(2):91-7.
48. Yamashita H, Tsukayama H, Hori N, Kimura T, Tanno Y. Incidence of adverse reactions associated with acupuncture. J Altern Complem Med. 2000;6(4):345-50.
49. Yamashita H, Tsukayama H, Tanno Y, Nishijo K. Adverse events in acupuncture and moxibustion treatment: A six-year survey at a national Clinic in Japan. J Altern Complem Med. 1999;5(3):229-36.
50. Zhao L, Zhang FW, Li Y, Wu X, Zheng H, Cheng LH, et al. Adverse events associated with acupuncture: Three multicentre randomized controlled trials of 1968 cases in China. Trials. 2011;12:no pagination.
51. Degner D, Grohmann R, Kropp S, Ruther E, Bender S, Engel RR, et al. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry. 2004;37 Suppl 1:S39-45.
52. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. American journal of therapeutics. 2000;7(2):115-21.
53. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. Bmj. 2011;342:c7086.
54. Martin Arias LH, Martin Gonzalez A, Sanz Fadrique R, Salgueiro Vazquez E. Gastrointestinal safety of coxibs: systematic review and meta-analysis of observational studies on selective inhibitors of cyclo-oxygenase 2. Fundamental & clinical pharmacology. 2018.
55. Wang C, Tan B, Williams A. Safety and side effects of acupuncture therapy in Australia: A systematic review. Eur J Integr Med. 2019.
56. Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. Pediatrics. 2011;128(6):e1575-87.
57. Wang CC, Tan JY, Williams A. Safety and side effects of acupuncture therapy in Australia: A systematic review. Eur J Integr Med. 2019;27:81-9.
58. Tan JY, Molassiotis A, Wang T, Suen LK. Adverse events of auricular therapy: a systematic review. Evid Based Complement Alternat Med. 2014;2014:506758.
59. Zhang J, Shang H, Gao X, Ernst E. Acupuncture-related adverse events: a systematic review of the Chinese literature. Bull World Health Organ. 2010;88(12):915-21C.
60. Xu S, Wang L, Cooper E, Zhang M, Manheimer E, Berman B, et al. Adverse events of acupuncture: a systematic review of case reports. Evid Based Complement Alternat Med. 2013;2013:581203.
61. He W, Zhao X, Li Y, Xi Q, Guo Y. Adverse events following acupuncture: a systematic review of the Chinese literature for the years 1956-2010. J Altern Complem Med. 2012;18(10):892-901.
62. Ernst E, Lee MS, Choi TY. Acupuncture: does it alleviate pain and are there serious risks? A review of reviews. Pain. 2011;152(4):755-64.
63. Ullah W, Ahmad A, Mukhtar M, Virk HUH, Sarwar U, Figueredo V. Acupuncture-Related Cardiac Complications: A Systematic Review. J Invasive Cardiol. 2019;31(4):E69-E72.
64. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ. 2006;333(7568):597-600.
65. Zhu HZ. Running a Safe and Successful Acupuncture Clinic. Edinburgh, London, New York, Oxford, Philadelphia, St Louis, Sydney, Toronto: Elsevier - Churchill Livingstone; 2006.
66. Deng L, Gan Y, He S, Ji X, Y. L, Wang R, et al. Chinese Acupuncture and Moxibustion. 2nd ed. Beijing, China: Foreign Languages Press; 1999.
67. Schwaneberg T, Witt CM, Roll S, Pach D. Comparing physicians' and patients' reporting on adverse reactions in randomized trials on acupuncture-a secondary data analysis. BMC Complement Altern Med. 2019;19(1):223.
68. Suissa S. Statistical methods in pharmacoepidemiology: advances and challenges. Stat Methods Med Res. 2009;18(1):3-6.
69. Capili B, Anastasi JK, Geiger JN. Adverse event reporting in acupuncture clinical trials focusing on pain. Clin J Pain. 2010;26(1):43-8.
70. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. Bmj. 2019;367:l5657.



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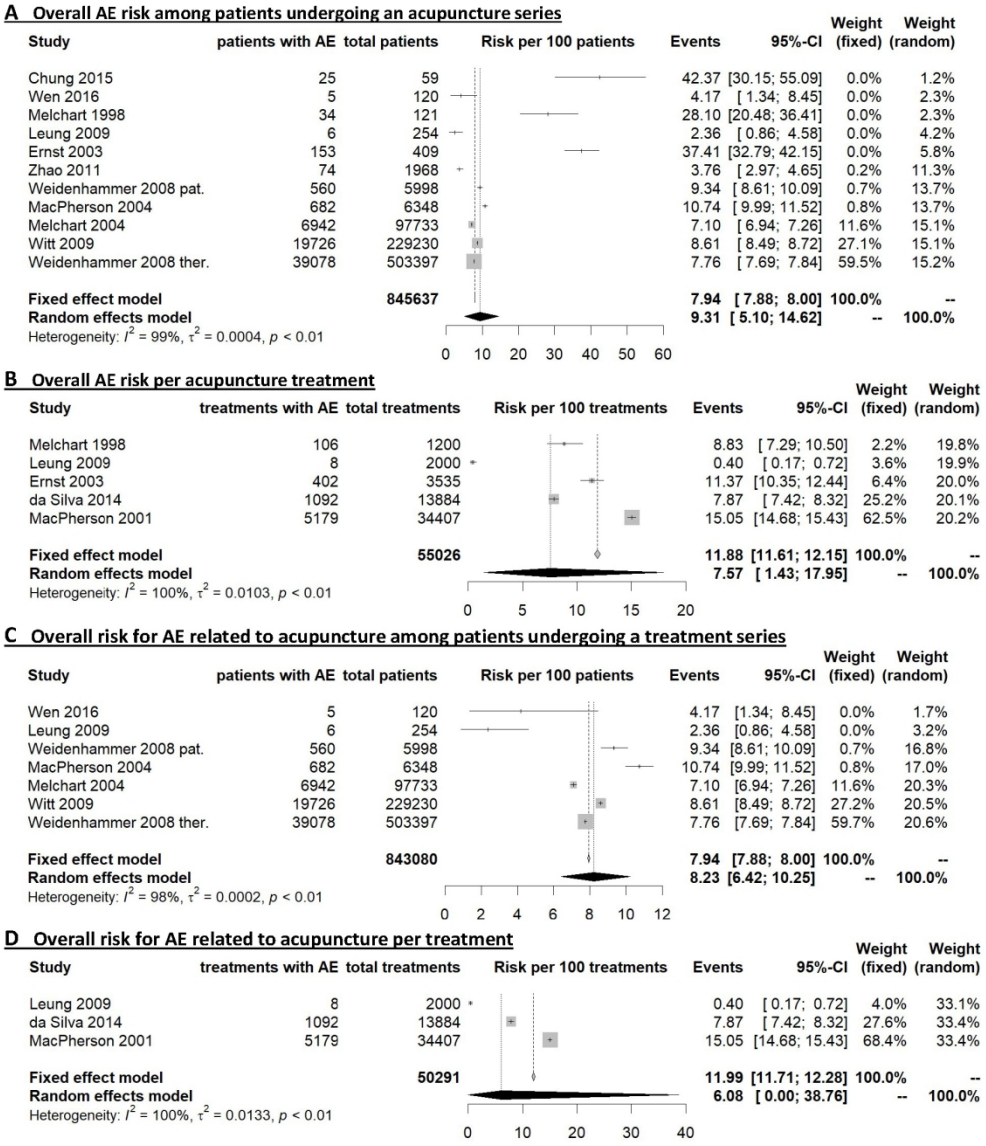

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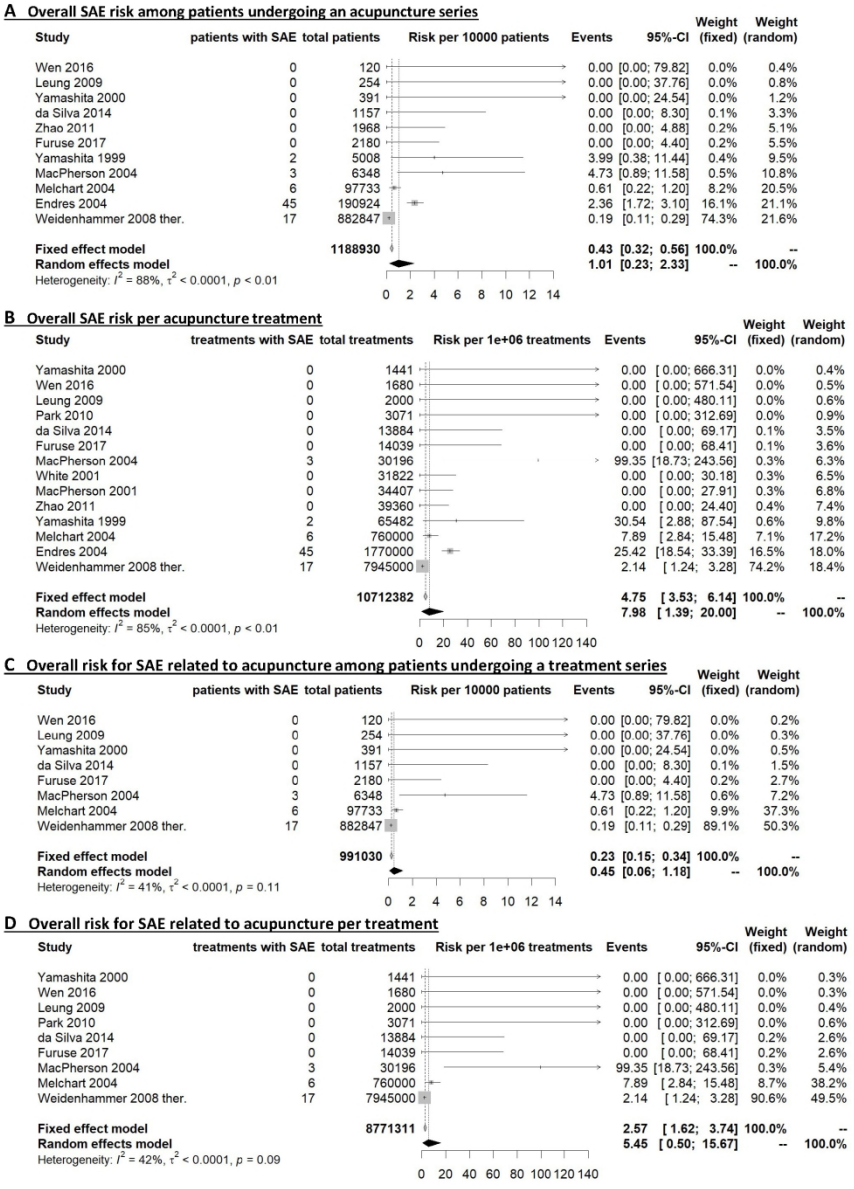

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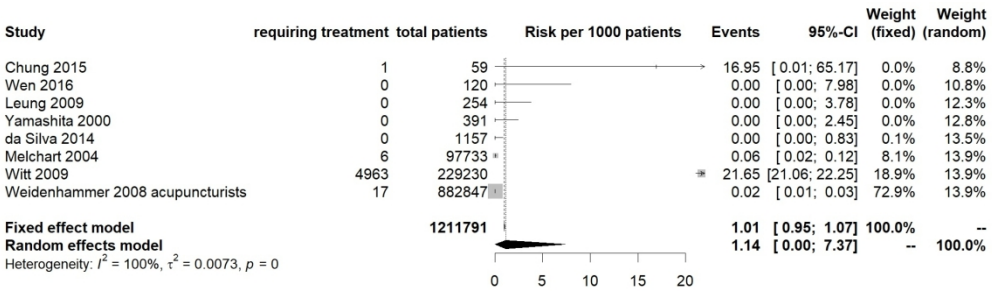

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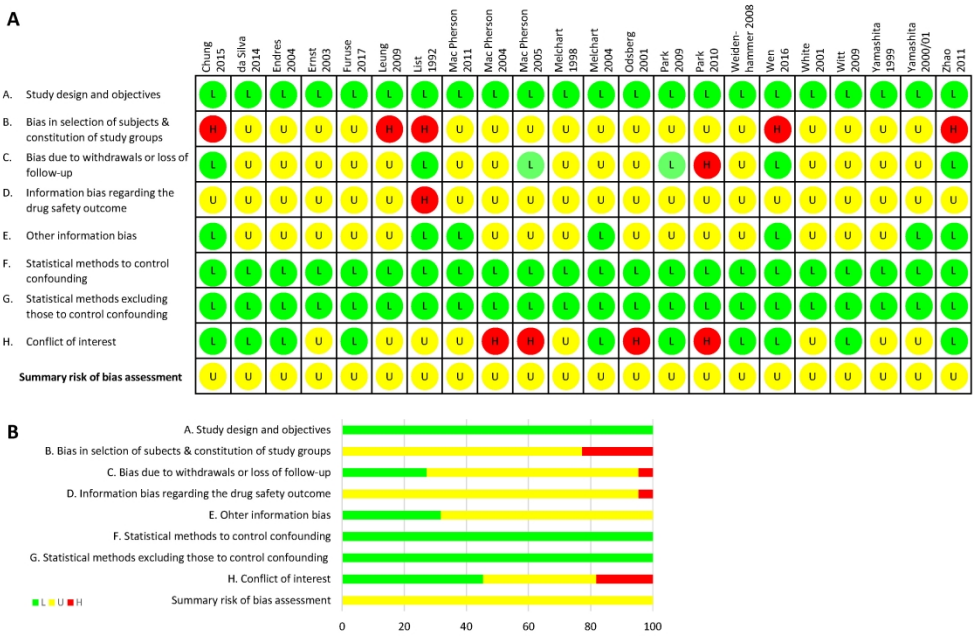

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PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Acupuncture related adverse events - a systematic review of prospective clinical trials

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

English

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.
19/09/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.
31/12/2019

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Piloting of the study selection process

Piloting of the study selection process

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Dr. Petra Bäumler

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Petra

7. * Named contact email.

Give the electronic email address of the named contact.

Petra.Baeumler@med.uni-muenchen.de

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Dr. Petra Bäumler

Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich

Pettenkoferstr. 8a

80336 Munich, Germany

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

0049-89-4400-53625

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Petra Baeumler. Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich
Professor Dominik Irnich. Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich
Mrs Theresa Stübinger. Multidisciplinary Pain Center, Department of Anaesthesiology, Universtiy Hospital LMU Munich

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

No funding is received

State the funder, grant or award number and the date of award

Grant number(s)

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

Yes

Petra Bäumler and Dominik Irnich receive honoraria and travel costs from non-profit academic organizations, physician chamber and universities for teaching and lecturing. Theresa Stübinger declares no conflict of interest

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Wenyue Zhang. School of Acupuncture, Moxibustion and Tuina, Beijing University of Chinese Medicine

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the risk for minor and serious adverse events caused by acupuncture?

What kind of adverse events can be caused by acupuncture?

What is the risk of the different types of acupuncture related adverse events?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Databases: PubMed, Scopus, EMBASE

Publication period: inception to 15th September 2019

Search Terms: acupuncture, adverse event(s), adverse effect(s)

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Acupuncture is the insertion of fine needles at certain points, so called acupuncture points, on the patients body for therapeutic or preventive purposes. Acupuncture originates from ancient Chinese medicine, but is nowadays used worldwide in many different variations. There is level 1 for its effectiveness in acute and chronic pain. Needles are stimulated manually, electrically. Often moxibustion is used as an adjunct. The safety of acupuncture has been debated, and surely needle penetration can cause harms, such as tissue damage, peripheral nerve injury and bleeding. In comparsion to analgesic drugs for example, risk and consequences of adverse events are deemed minor, but reviews on the safety of acupuncture are either outdated or lack an assessment of study quality.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Humans treated by needle acupuncture

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Acupuncture involving either manual or electrical needle stimulation with or without moxibustion

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

As the aim of this review is to estimate the crude risk of acupuncture related adverse events, comparator group data are not relevant.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Inclusion criteria:

Prospective study

Primary outcome is the risk of acupuncture related adverse events

Treatment involves acupuncture with needles that are stimulated manually or electrically either in combination with or without moxibustion

Articles published in English or German before 15th of September 2019

Exclusion criteria

Treatment involves injection

Treatment involves skin penetration with any other device than classcial acupuncture needles such as press needles, cauterization devices etc.

Treatment is restricted to non-penetrating stimulation such as laser acupuncture, acupressure, transcutaneous electrical nerve stimulation or moxibustion

Treatment is restricted to particular body parts associated with low risk of adverse events such as auricular or one-point acupuncture

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Risk of serious and minor acupuncture related adverse events (AE) as number of AE per treatment and patients with AE per 100.000 patients treated

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

adverse events ocurring during or after acupuncture treatment

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Type of adverse events caused by acupuncture

Risk of the different types of acupuncture related adverse-events

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

adverse Events ocurring during or after acupuncture treatment

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Incidence of acupuncture related adverse events will be extracted as the number of adverse events per treatment and as number of patients experiencing these adverse events per the total number of patients treated. Data extraction will be performed by two independent reviewers who will extract all available data on acupuncture related adverse events from identified studies. This includes extraction of the total number of and/or patients with minor and serious adverse events as well as extraction of the numbers of and/ or patients with all types of adverse events separately in relation to the number of treatments and/or total number of patients treated. The different types of adverse events will be categorized into supersets of adverse events whose risk is calculated separately.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Included studies will be assessed for risk of bias according to a checklist developed by Faillie and colleagues for systematic reviews focusing on adverse events.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will provide the reader with the range (min and max) and the median of the total risk to suffer from an minor and serious adverse event during or after acupuncture treatment that was identified by the studies. The same measures will be provided for the risks of the supersets of adverse events identified from the different studies.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

It is likely that certain subsets of patients are at a higher risk for acupuncture related adverse events. According to the obtained results we will provide characteristics and separate summaries of studies including patients with a high and low risk profile.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews

No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
Yes

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.
Germany

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

The review has not been registered elsewhere.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

A paper presenting the review results will be submitted to a journal listed in MEDLINE. Furtermore, results will be published at international congresses.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

acupuncture, adverse-event, adverse-effect, safety, needling, moxibustion, traditional Chinese mecicine

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint. List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3 / 19
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 - 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4 - 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4 - 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 Figure 5A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2-4 Table 2-3 Suppl. App. S2 - S3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 - 12 Figure 2-4 Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 Figure 5 B
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8 - 12 Figures 2C/D 3C/D
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

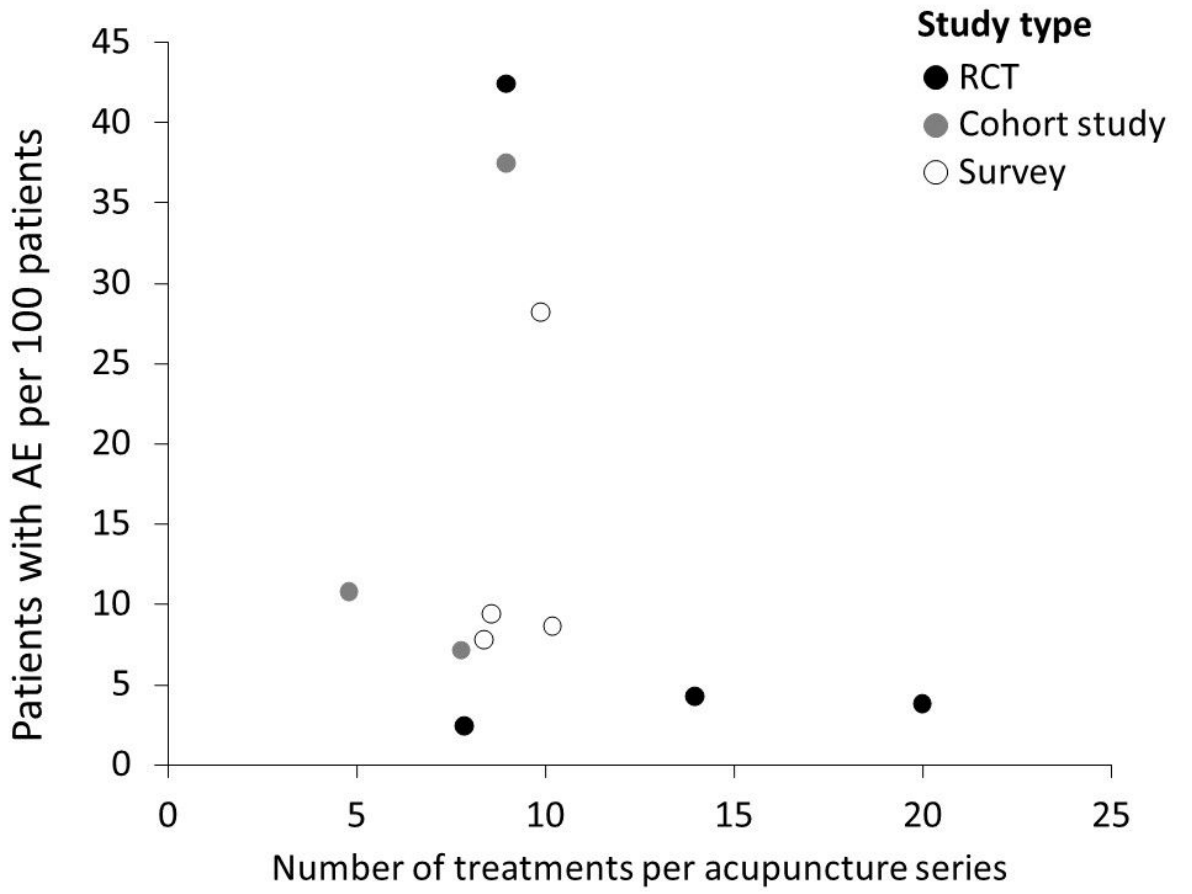
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Bleeding		
• Bleeding • Bleeding at needling site • Mild / transient / minor bleeding • Subcutaneous bleeding • Hematoma • Minor hematoma • Subcutaneous / superficial hematoma	• Small hemorrhage • Lesion of blood vessel • Bruising • Bruising at needling site • Mild / transient bruising • Heavy bruising • Subcutaneous bruise	• Ecchymosis or hematoma accompanied by pain • Ecchymosis or hematoma without pain • Petechia or ecchymosis
Local pain		
• Pain • Needle (-site) pain • Pain where needle was inserted / at the site of the needle / in the punctured region • Mild / transient pain at needling site • Severe / strong / significant pain at needling site	• Pain upon insertion / stimulation • Pain while needle was in place • Pain upon needle withdrawal at the acupuncture point • Pain after needle was removed • Remaining / residual needle site pain • Prolonged / unacceptable pain at needle site	• Mild pain at the acupuncture site more than one hour after treatment • Pain disappearing after > 3 days • Chest pain (pneumothorax ruled out) • Electroacupuncture problems e.g. too strong current resulting in pain • Local muscle pain • Unknown pain
Other local AE		
• Wheal • (Local) swelling • Redness • Flare • Localized erythema • Needle-site / local skin reaction • (Skin) irritation at acupuncture point • Skin infection • Local (skin) infection	• Inflammation at application site • Itch • Itching and redness • Itching in the punctured region • Itching and erythema (suspected contact dermatitis) • Local allergic reaction (uticaria) • Needle allergy • Allergic phenomena / reaction	• Significant rash on abdomen few days after acupuncture • Cellulitis after treatment of edematous leg • Edema in m. tibialis with anterior toe lifting weakness (fully resolved) • Other local AE (around the acupuncture site)
Central nervous system		
• Aphasia • Dizziness • Mild / transient dizziness • Imbalance • Severe dizziness, vertigo or loss of balance	• Vertigo • Disorientation (length unspecified, 1 h, 1 day) • Severe disorientation • Disturbed speech • Slurred speech	• Disturbed vision • Spontaneous sensory perceptions • Shivering • Seizure shortly after treatment • Tremor
Peripheral nervous system		
• Cold sensation at needling site • Feeling of acupuncture point at contralateral arm • Paraesthesia • Temporary paraesthesia • Tingling • Tingling, prickling, burning, dysesthesia	• Prolonged deqi • Strong acupuncture or heavy sensation • Hypaesthesia • Numbness • Numbness in upper extremity • Numbness and unusual sensation • Severe stiffness or numbness	• Hypaesthesia with numbness for three days • Insensibility • Itching, pins & needles, tingling or burning sensation • Nerve irritation • Neuritis
Aggravation of symptoms		
• Aggravation • Aggravation of complaints / existing ailment / existing symptoms • Unexpected, severe or prolonged worsening of symptoms • Aggravation of symptoms during acupuncture session / after treatment	• Transient aggravation of symptoms • Aggravation of existing symptoms followed by improvement • Deterioration / exacerbation of symptoms • General aggravation of symptoms • Worsening of health state	• Worsening of condition (after removing needles) • Headache and or facial pain • pressure and or tension in the teeth • Increased pain
Vegetative nervous system		
• (Generalized) sweating • Isolated sweating of hands • Mild sweating • Flushed cheeks and body warmth • Hot flash • Feeling of warm / heat / cold • Coldness / feeling cold • Freezing • (Feeling of) fatigue • Extreme feeling of fatigue • Feeling tired (mild transient) • Tiredness and exhaustion	• Abnormal tiredness • Severe / significant tiredness or exhaustion • Lethargy • Dazed • Vasovagal reaction: collapse, dizziness, nausea & vomiting • Unconsciousness • Fainting • Faint / dizzy • Feel faint / drowsy • Feel faint (significant)	• Significant / severe drowsiness • Drowsiness not causing hazard • Prolonged drowsiness (one day, one week) • Drowsiness or restlessness • Orthostatic problems • Malaise • Poor concentration • Dry lips / mouth • Xerostomia • Hunger / thirst

Motor system		
• Cramp	• Heavy legs	• Joint problems
• General muscle tenderness	• Knee went weak	• Restricted movement
• Muscle spasm / tension / weakness	• Weakness in legs / legs or arms	• Stiffness
Distant pain		
• Pain / ache / discomfort other than at needling site	• Mild transient pain not at needling site	• Generalized muscle pain
• Reactive pain at other body sites	• Chest pain / tightness	• Other / unspecified pain / aches
Gastrointestinal / gynaecological system		
• Nausea	• Tiredness next day after ten hours of diarrhoea (significant)	• Increased peristalsis
• Mild and transient nausea	• Stomach ache	• Loss of appetite
• Severe nausea	• Abdominal distension	• Other gastrointestinal complaints
• Vomiting	• Impaired bowel function	• Increased haemorrhage during menses
• Severe vomiting	• Digestive problems	• Menstrual problems
• Constipation	• Entero- / gastrospasm	
• Diarrhoea		
Cardiovascular system		
• Cardiovascular / circulatory problems	• Increase in blood pressure	• Tachycardia
• Depression of blood pressure	• Palpitation	• Other cardiac disturbances
Respiratory system		
• Asthma attack	• Breathing difficulties	• Bronchitis or airway problems
Generalized skin reactions		
• Dermatological problems	• Other dermatological phenomena	
Headache		
• Headache	• Headache for three days	• Severe headache or migraine
• Headache the next day	• Migraine attack	
Emotional interference		
• Aggressive behaviour	• Depressive mood	• Severe emotional outburst and anger at practitioner
• Anxiety	• Discomfort	• Fear
• Anxiety and panic (up to one hour)	• Restlessness or nervousness	• Grief / crying / tearful
• Significant panic with sensation of heat and sweatiness	• Disorientation, anxiety, nervousness, insomnia or emotional	• Needle phobia, anxiety and rage
• Severe panic / agitation / depression with anxiety	• Emotional /psychological reaction	• (Severe) nightmares
• Depressed emotional state or neurovegetative dystonia	• (Uncontrolled) euphoria	• Other mood swings
	• Significant emotional release (manic, relaxed, rage or confusion)	
Sleeping problems		
• Sleep disturbances	• Severe sleeping problems	• Insomnia
• Impaired sleep	• Severe sleeplessness	
Moxa caused adverse events		
• Burn injury	• Burns	• Blister following moxibustion
Needling malpractice		
• Left alone / unattended in the treatment room for too long	• Failure to remove needle(s)	
• Broken needle	• Forgotten / dropped needle	
• Stuck or bent needle	• Needle lost or forgotten	
Other or unclassified adverse events		
• Change of symptoms	• Nose bleeding	• Additional comments
• Illness	• Miscellaneous symptoms	• Other systematic symptoms
• Sick	• Haematuria on next day	• Other neurological problems
• (Systemic) infection	• Increased urinary frequency	• Others / unspecified / other (mild) adverse events
• Fever	• Concomitant diseases of recent appearance	• other negative reactions
• Angina	• Change of taste	• Unknown due to incomplete record form
• Eye irritation	• Change of weight / weight reduction	
• Irritated tongue		

Online supplementary appendix S3: Categorization of adverse events

Subheadings represent the categories to which adverse events (AE) were assigned. AE descriptors extracted from the included publication are reported verbatim or in spirit in order to provide an overview of the different wordings concerning AE type and severity. Slashes indicate that expressions were also used separately. Terms in brackets indicate that such terms were not used in all of the descriptors with otherwise similar wording.



Online supplementary appendix S4: Independence of incidences of adverse events per patient from the number of treatments per acupuncture series and study type

Scatterplot of the number of treatments applied within an acupuncture series against the observed adverse events (AE) incidence as patients with AE per 100 patients

Study	Total number of patients	Risk as patients with AE per 100 patients [95%-CI]									
		Bleeding	Needle sit pain	Other local AE	Vegetative reaction	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal / gynaecologcial system	Unclassified AE
List 1992	29		44.83 [27.46; 62.87]		58.62 [40.52; 75.59]	93.10 [81.26; 99.30]	37.93 [21.45; 55.99]	27.59 [13.14; 44.96]		17.24 [5.94; 32.83]	3.45 [0.00; 12.99]
Chung 2015	59	15.25 [7.30; 25.45]	32.20 [20.99; 44.57]	35.59 [23.97; 48.14]	13.56 [6.10; 23.38]		5.08 [0.99; 12.08]	11.86 [4.94; 21.26]		5.08 [0.99; 12.08]	3.39 [0.33; 9.47]
Wen 2016	120	0.83 [0.00; 3.24]	2.50 [0.48; 6.04]						0.83 [0.00; 3.24]		
Melchart 1998	121	3.31 [0.88; 7.21]	14.05 [8.46; 20.78]	1.65 [0.16; 4.68]	8.26 [4.05; 13.81]	10.74 [5.88; 16.85]	2.48 [0.48; 5.99]	0.83 [0.00; 3.21]	0.83 [0.00; 3.21]	4.13 [1.33; 8.39]	
Leung 2009	254	2.36 [0.86; 4.58]									
Yamashita 2000	391		0.26 [0.00; 1.00]	1.02 [0.27; 2.26]	11.76 [8.76; 15.14]	2.81 [1.41; 4.68]	0.77 [0.15; 1.87]				
Ernst 2003	409	25.18 [21.10; 29.50]	8.07 [5.63; 10.90]	0.24 [0.00; 0.96]	6.36 [4.20; 8.92]	0.98 [0.26; 2.16]	6.11 [4.00; 8.64]	4.89 [3.01; 7.19]		1.96 [0.84; 3.52]	17.85 [14.29; 21.70]
Zhao 2011	1968	3.40 [2.65; 4.25]	0.05 [0.00; 0.20]		0.10 [0.01; 0.29]		0.05 [0.00; 0.20]			0.05 [0.00; 0.20]	
Furuse 2017	2180	12.80 [11.43; 14.23]	6.24 [5.26; 7.29]			1.06 [0.67; 1.53]					1.10 [0.71; 1.58]
Weidenhammer 2008 pat.	5998	0.48 [0.32; 0.67]	0.32 [0.19; 0.47]	0.32 [0.19; 0.47]	2.72 [2.32; 3.14]	0.80 [0.59; 1.04]	0.90 [0.68; 1.16]	0.47 [0.31; 0.66]	0.95 [0.72; 1.21]	0.62 [0.43; 0.83]	0.47 [0.31; 0.66]
MacPherson 2004	6348	0.58 [0.41; 0.79]	1.86 [1.54; 2.21]	0.36 [0.23; 0.53]	4.69 [4.19; 5.23]	1.20 [0.94; 1.48]	0.87 [0.65; 1.11]	0.65 [0.46; 0.86]	0.17 [0.09; 0.29]	0.96 [0.74; 1.22]	0.38 [0.24; 0.54]
Melchart 2004	97733	4.56 [4.43; 4.70]	3.28 [3.17; 3.39]	0.18 [0.15; 0.20]	0.48 [0.44; 0.53]	0.12 [0.10; 0.14]					0.33 [0.29; 0.36]
Endres 2004	190924	5.18 [5.08; 5.28]	0.05 [0.04; 0.06]	24.51 [24.31; 24.70]	0.70 [0.67; 0.74]	1.31 [1.26; 1.36]		0.08 [0.07; 0.10]			0.07 [0.05; 0.08]
Witt 2009	229230	6.15 [6.05; 6.24]	0.45 [0.43; 0.48]	0.60 [0.57; 0.63]	0.30 [0.28; 0.33]	0.40 [0.38; 0.43]	0.26 [0.24; 0.28]	0.26 [0.24; 0.28]	0.76 [0.72; 0.79]	0.22 [0.20; 0.24]	0.11 [0.10; 0.12]
Weidenhammer 2008 therap.	503397	4.84 [4.78; 4.90]	3.95 [3.90; 4.01]	0.15 [0.14; 0.16]	0.08 [0.07; 0.08]	0.08 [0.07; 0.09]				0.01 [0.01; 0.02]	0.26 [0.25; 0.28]
Fixed effect		5.09 [5.05; 5.13]	1.81 [1.78; 1.84]	1.85 [1.83; 1.88]	0.25 [0.24; 0.26]	0.29 [0.28; 0.30]	0.28 [0.26; 0.31]	0.18 [0.17; 0.19]	0.74 [0.71; 0.77]	0.06 [0.05; 0.06]	0.19 [0.18; 0.20]
Random effect		4.67 [2.08; 8.22]	3.75 [0.74; 8.94]	2.79 [0.02; 10.01]	1.95 [0.40; 4.63]	1.48 [0.00; 5.90]	1.45 [0.07; 4.51]	0.69 [0.02; 2.34]	0.60 [0.21; 1.20]	0.60 [0.04; 1.81]	0.57 [0.01; 1.95]
tau^2		0.0008	0.0085	0.0494	0.0012	0.0017	0.0018	0.0004	0.0005	0.0008	0.0003
I^2		99.4% [99.3%; 99.5%]	99.9% [99.9%; 99.9%]	100.0% [100.0%; 100.0%]	99.7% [99.7%; 99.7%]	99.8% [99.8%; 99.8%]	96.3% [94.6%; 97.5%]	98.1% [97.4%; 98.7%]	92.6% [85.7%; 96.2%]	99.3% [99.1%; 99.4%]	99.0% [98.7%; 99.2%]
p-value Q-test		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Study	Total number of patients	Risk as patients with AE per 100 patients [95%-CI]								
		Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
List 1992	29			41,38 [24,41; 59,48]				20,69 [8,19; 37,03]		
Chung 2015	59	13.56 [6.0980; 23.38]			1,69 [0,00; 6,52]	0,00 [0,00; 1,62]				
Wen 2016	120									
Melchart 1998	121		0.83 [0.00; 3.21]				0,83 [0,00; 3,21]			
Leung 2009	254									
Yamashita 2000	391	0.51 [0.0485; 1.46]								
Ernst 2003	409	0.49 [0.0463; 1.40]	0.49 [0.05; 1.40]	0,24 [0,00; 0,96]			0,98 [0,26; 2,16]			0,24 [0,00; 0,96]
Zhao 2011	1968			0,10 [0,01; 0,29]						
Furuse 2017	2180	0.05 [0.0000; 0.18]				0,60 [0,32; 0,96]			0,96 [0,60; 1,42]	
Weidenhammer 2008 pat.	5998	1.37 [1.0889; 1.68]	0.60 [0.42; 0.81]	0,35 [0,22; 0,52]				0,13 [0,06; 0,24]		0,07 [0,02; 0,15]
MacPherson 2004	6348	1.21 [0.9585; 1.50]				1,04 [0,81; 1,30]	1,24 [0,99; 1,53]	0,74 [0,54; 0,97]	0,44 [0,29; 0,62]	
Melchart 2004	97733	0.04 [0.0275; 0.05]				0,25 [0,22; 0,28]				
Endres 2004	190924					0,00 [0,00; 0,00]	0,04 [0,03; 0,05]	0,04 [0,03; 0,05]	0,00 [0,00; 0,00]	
Witt 2009	229230	0.52 [0.4944; 0.55]	0.27 [0.25; 0.29]	0,08 [0,07; 0,09]	0,09 [0,08; 0,10]	0,01 [0,00; 0,01]	0,09 [0,08; 0,11]	0,04 [0,03; 0,05]	0,01 [0,00; 0,01]	0,02 [0,01; 0,02]
Weidenhammer 2008 therap.	503397	0.03 [0.0287; 0.04]	0.42 [0.40; 0.43]			0,28 [0,27; 0,30]	, 0,0197 [0,02; 0,02]			
Fixed effect		0.12 [0.11; 0.13]		0,09 [0,08; 0,10]	0,09 [0,08; 0,10]	0,11 [0,11; 0,12]	0,04 [0,04; 0,04]	0,05 [0,04; 0,05]	0,00 [0,00; 0,01]	0,02 [0,01; 0,02]
Random effect		0.51 [0.03; 1.55]	0.40 [0.24; 0.61]	0,38 [0,00; 4,79]	0,35 [0,00; 35,67]	0,22 [0,01; 0,67]	0,20 [0,00; 0,81]	0,16 [0,00; 0,91]	0,14 [0,00; 1,16]	0,04 [0,00; 0,26]
tau²		0.0012	0.0001	0.0011	0.0029	0.0009	0.0002	0.0001	0.0002	0.0001
I²		99.6% [99.6%; 99.7%]	96.4% [93.9%; 97.9%]	94.6% [90.2%; 97.1%]	= 58.2% [0.0%; 90.1%]	99.7% [99.7%; 99.8%]	98.7% [98.2%; 99.1%]	97.1% [95.3%; 98.2%]	98.3% [97.3%; 99.0%]	69.0% [0.0%; 91.0%]
p-value Q-test		< 0.0001	< 0.0001	< 0.0001	0.1221	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0398

Online supplementary appendix S5: Risks for different types of adverse events per 100 patients undergoing an acupuncture series as reported in single studies

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses displayed in table 4

Study	Total number of treatments	Risk as treatments with AE per 100 treatments [95%-CI]									
		Bleeding	Pain	Other local AE	Vegetative nervous system	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal /gynaecologcial AE	Unclassified AE
Yamashita 2000	1441	45.45 [42.89; 48.03]	15.75 [13.92; 17.68]	0.90 [0.48; 1.46]	4.72 [3.69; 5.87]	1.11 [0.63; 1.72]	0.35 [0.11; 0.72]		0.07 [0.00; 0.27]		
daSilva 2014	13884	4.11 [3.79; 4.45]	3.02 [2.74; 3.31]	0.43 [0.33; 0.55]	0.02 [0.00; 0.05]		0.01 [0.00; 0.03]	0.11 [0.06; 0.17]		0.04 [0.01; 0.07]	
Melchart 1998	1200	0.33 [0.09; 0.74]	4.17 [3.11; 5.37]	0.17 [0.02; 0.48]	2.58 [1.76; 3.56]	1.75 [1.09; 2.57]	0.25 [0.05; 0.61]	0.08 [0.00; 0.33]	0.08 [0.00; 0.33]	0.42 [0.13; 0.86]	
MacPherson 2005	9408	4.72 [4.30; 5.16]	12.27 [11.61; 12.94]	0.26 [0.16; 0.37]	27.87 [26.97; 28.78]	1.75 [1.50; 2.03]		0.35 [0.24; 0.48]	4.49 [4.08; 4.91]	1.18 [0.97; 1.41]	0.35 [0.24; 0.48]
Furuse 2017	14039	3.16 [2.88; 3.46]	1.25 [1.07; 1.44]	0.09 [0.04; 0.14]	0.63 [0.51; 0.77]	0.20 [0.13; 0.28]	0.09 [0.05; 0.15]	0.07 [0.03; 0.12]		0.10 [0.05; 0.16]	0.20 [0.13; 0.28]
Ernst 2003	3535	5.18 [4.47; 5.93]	1.30 [0.95; 1.70]	0.08 [0.02; 0.21]	2.46 [1.98; 3.00]	0.25 [0.12; 0.45]	1.08 [0.76; 1.44]	1.44 [1.08; 1.86]		0.34 [0.17; 0.56]	5.46 [4.74; 6.23]
Odsberg 2001	9277	18.44 [17.66; 19.24]	0.08 [0.03; 0.14]	0.05 [0.02; 0.11]	1.42 [1.19; 1.67]	2.33 [2.03; 2.65]	0.18 [0.11; 0.28]	0.01 [0.00; 0.04]		0.02 [0.00; 0.06]	0.06 [0.02; 0.13]
Yamashita 1999	65482	0.03 [0.02; 0.05]	0.01 [0.00; 0.02]	0.00 [0.00; 0.01]	0.00 [0.00; 0.01]	0.00 [0.00; 0.01]	0.01 [0.00; 0.02]	0.00 [0.00; 0.01]		0.01 [0.00; 0.02]	0.00 [0.00; 0.01]
Park 2009	1095	8.40 [6.83; 10.12]	3.38 [2.39; 4.53]		3.11 [2.16; 4.21]		0.82 [0.37; 1.44]	1.46 [0.84; 2.26]			0.46 [0.14; 0.94]
Leung 2009	2000	0.40 [0.17; 0.72]									
Park 2010	3071	1.95 [1.49; 2.47]	0.49 [0.27; 0.77]	0.10 [0.02; 0.24]	0.75 [0.66; 0.85]	0.07 [0.01; 0.19]	0.03 [0.00; 0.13]	0.26 [0.11; 0.47]		0.03 [0.00; 0.13]	0.03 [0.00; 0.13]
White 2001	31822	3.09 [2.90; 3.28]	1.15 [1.04; 1.27]	0.10 [0.07; 0.13]	4.73 [4.50; 4.95]	0.98 [0.87; 1.09]	0.01 [0.00; 0.03]	0.00 [0.00; 0.01]		0.02 [0.01; 0.04]	0.46 [0.39; 0.54]
MacPherson 2001	34407	2.08 [1.93; 2.23]	1.24 [1.12; 1.35]	0.01 [0.00; 0.02]	4.73 [4.50; 4.95]	2.83 [2.66; 3.01]	0.63 [0.55; 0.71]		0.51 [0.44; 0.59]	0.31 [0.25; 0.37]	0.86 [0.76; 0.96]
Fixed effect		1.87 [1.80; 1.93]	0.82 [0.78; 0.87]	0.05 [0.04; 0.06]	1.08 [1.04; 1.13]	0.58 [0.55; 0.62]	0.09 [0.07; 0.10]	0.03 [0.02; 0.04]	0.96 [0.87; 1.05]	0.08 [0.07; 0.09]	0.23 [0.20; 0.25]
Random effect		4.92 [1.18; 11.01]	2.43 [0.63; 5.35]	0.13 [0.04; 0.27]	2.24 [0.21; 6.35]	0.84 [0.26; 1.75]	0.20 [0.05; 0.46]	0.19 [0.02; 0.55]	0.73 [0.00; 5.02]	0.15 [0.03; 0.38]	0.47 [0.03; 1.46]
tau^2		0.0169	0.0095	0.0004	0.0213	0.0055	0.0011	0.0008	0.0085	0.0008	0.0025
I^2		99.9% [99.9%; 99.9%]	99.8% [99.8%; 99.8%]	96.4% [94.9%; 97.4%]	99.9% [99.9%; 99.9%]	99.7% [99.6%; 99.7%]	98.4% [97.9%; 98.8%]	97.5% [96.6%; 98.2%]	99.5% [99.4%; 99.7%]	98.2% [97.6%; 98.6%]	99.4% [99.2%; 99.5%]
p-value Q-test		< 0.0001	< 0.0001	0.0001	< 0.0001	< 0.0001	0.0001	< 0.0001	0.0001	0.0001	0.0001

Study	Total number of treatments	Risk as treatments with AE per 100 treatments [95%-CI]								
		Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
Yamashita2000	1441	0.14 [0.01; 0.40]				0.62 [0.28; 1.10]				
daSilva2014	13884					0.24 [0.16; 0.33]				
Melchart1998	1200		0.08 [0.00; 0.33]				0.08 [0.00; 0.33]			
MacPherson2005	9408						0.67 [0.51; 0.84]			
Furuse2017	14039	0.01 [0.00; 0.03]	0.01 [0.00; 0.04]			0.10 [0.05; 0.16]			0.17 [0.11; 0.25]	
Ernst2003	3535	0.06 [0.01; 0.16]	0.06 [0.01; 0.16]	0.03 [0.00; 0.11]			0.11 [0.03; 0.25]			0.03 [0.00; 0.11]
Odsberg2001	9277	0.05 [0.02; 0.11]		0.01 [0.00; 0.04]			0.04 [0.01; 0.10]			
Yamashita1999	65482					0.04 [0.03; 0.06]	0.01 [0.00; 0.02]		0.01 [0.00; 0.02]	
Park2009	1095									
Leung2009	2000									
Park2010	3071	0.03 [0.00; 0.13]		0.10 [0.02; 0.24]		0.10 [0.02; 0.24]				
White2001	31822	0.11 [0.08; 0.15]		0.00 [0.00; 0.01]		0.15 [0.11; 0.19]	0.01 [0.00; 0.02]		0.00 [0.00; 0.01]	
MacPherson2001	34407	0.00 [0.00; 0.01]		0.00 [0.00; 0.01]		0.01 [0.00; 0.02]	0.01 [0.00; 0.03]		0.00 [0.00; 0.01]	
Fixed effect		0.03 [0.02; 0.05]	0.02 [0.01; 0.05]	0.01 [0.00; 0.01]		0.06 [0.05; 0.08]	0.03 [0.02; 0.03]		0.01 [0.01; 0.02]	
Random effect		0.04 [0.01; 0.10]	0.03 [0.00; 0.13]	0.01 [0.00; 0.04]		0.12 [0.02; 0.28]	0.08 [0.00; 0.27]		0.02 [0.00; 0.18]	0.03 [0.00; 0.11]
tau²		0.0002	0.0001	0.0001		0.0002	0.0004		0.0001	
I²		90.3% [82.5%; 94.6%]	21.2% [0.0%; 91.8%]	58.1% [0.0%; 84.4%]		95.1% [92.0%; 96.9%]	96.8% [95.1%; 97.9%]		95.0% [90.3%; 97.5%]	
p-value Q-test		0.0001	0.2811	0.0489		0.0001	0.0001		0.0001	

Online supplementary appendix S6: Risks for different types of adverse events per 100 treatments as reported in single studies

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses displayed in table 4

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Acupuncture related adverse events – systematic review and meta-analyses of prospective clinical studies

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Abstract

Objective

Overview on risks for acupuncture related adverse events (AE).

Design

Systematic review and meta-analysis of prospective studies.

Data sources

Pubmed, Scopus, and EMBASE from inception date to September 15, 2019.

Eligibility criteria for selecting studies

Prospective studies assessing AE caused by needle acupuncture in humans as primary outcome published in English or German

Data extraction and synthesis

Two independent researchers selected articles, extracted the data and assessed study quality. Overall risks and risks for different AE categories were obtained from random effects meta-analyses.

Main outcomes

Overall risk for minor AE and serious AE (SAE) per patients and per treatments

Results

Out of 7679 screened articles 22 reporting on 21 studies were included. Meta-analyses suggest at least one AE occurring in 9.31% (95%-CI 5.10 to 14.62; 11 studies) of patients undergoing an acupuncture series and in 7.57% (95%-CI 1.43 to 17.95; 5 studies) of treatments. Summary risk estimates for SAE were 1.01 (95%-CI 0.23 to 2.33; 11 studies) per 10,000 patients and 7.98 (95%-CI 1.39 to 20.00; 14 studies) per 1 million treatments, for AE requiring treatment 1.14 (95%-CI 0.00 to 7.37; eight studies) per 1000 patients. Heterogeneity was substantial (I^2>80%). On average 9.4 AE occurred in 100 treatments of which half were bleeding, pain, or flare at the needle site argued to represent intended acupuncture reaction. AE definitions and assessments varied largely.

Conclusion

Acupuncture can be considered among the safer treatments in medicine. SAE are rare, and most common minor AE are very mild. AE requiring medical management are uncommon, but necessitate medical competence to assure patient safety. Clinical and methodological heterogeneity call for standardized AE assessments tools, clear criteria for differentiating acupuncture related AE from therapeutically desired reactions, and identification of patient related risk factors for AE.

PROSPERO registration number

CRD42020151930

Keywords

Adverse effects, adverse reactions, meta-analysis, safety, risk, pneumothorax

Strengths and limitations of this study

- First systematic review on acupuncture related adverse events including a risk of bias assessment
- First meta-analyses on adverse events related to acupuncture
- Complying with PRISMA guidelines
- Combining studies with heterogeneous AE definitions, but providing respective sensitivity analyses
- Causality assessment based on descriptions of adverse events as available from the included articles

Introduction

Acupuncture describes the insertion of fine needles at defined points on the patients' body for therapeutic or preventive purposes. It is used worldwide with growing popularity. In the EU acupuncture was identified as the most frequently provided method of complementary and alternative medicine (CAM) with 80,000 physicians and 16,380 non-medical practitioners.(1) In the UK alone 2.3 million traditional acupuncture treatments are carried each year.(2) In the US the number of acupuncturists doubled between 2002 and 2012.(3) The effectiveness of acupuncture is supported by level 1a evidence e.g. for chronic musculoskeletal pain and headache,(4-6) post-operative pain,(7, 8) post-operative nausea and vomiting,(9) as well as allergic rhinitis.(10) Furthermore, promising evidence exists for its potential role in the treatment of a large number of additional indications such as stroke rehabilitation,(11) depression,(12) aromatase inhibitor induced arthralgia,(13) and asthma.(14) Thus, acupuncture offers a non-pharmacological treatment option for various highly prevalent conditions with great disease burden and significant health economic impact. Long-term pharmacological treatment of these conditions is often associated with substantial side effects.(15, 16) Consequently, also risk estimates on acupuncture related adverse events (AE) are required for evidence-based risk benefit considerations that are essential for clinical decision making.

However, uncertainty remains about acupuncture safety. AE related to acupuncture are repeatedly and controversially discussed both in scientific literature as well as in public media. An overview of systematic reviews in 2017 (17) illustrates that many of the previous reviews on the safety of acupuncture just summarized case reports or case series. In turn, those reviews including studies that do allow for AE frequency estimation, such as cohort studies and large RCTs, mostly only addressed certain types of AE, particular patient groups, restricted acupuncture regimens, or certain countries. These data are surely important for clinical decision making in particular cases, but leave the overall risk of acupuncture related AE in the general population obscure. Additionally, debate exists about differentiating AE from therapeutically intended reactions that are claimed to form part of the acupuncture treatment. For example, international consensus exists that aggravation of symptoms represents an AE, since disease burden increases, although transient worsening of symptoms followed by long-term improvements can be interpreted as a so called healing crisis in complementary and alternative medicine.(18) In contrast, such consensus is still missing for local reactions such as small bleedings upon needle withdrawal, needling pain, and flare around the needling site. These are also referred to as beneficial signs by acupuncture experts and in standard text books and have been linked to neurophysiological mechanisms of acupuncture, suggesting that quality and intensity of these events should be considered when classifying them as AE.(19-21)

The last review on prospective studies on AE related to acupuncture with high external validity dates back to 2001,(22) did not meta-analytically summarize AE risk estimates and did not assess the quality of included studies. In addition, inconsistency and incompleteness of reporting in primary studies hampered the drawing of firm conclusions on acupuncture safety. Since then various large-scale clinical trials and nationwide surveys on acupuncture safety have been conducted.

Therefore, it was the aim of this review to provide an up to date summary of prospective trials that were particularly designed to evaluate AE related to needle acupuncture with manual or electrical stimulation in combination with or without moxibustion.

Methods

We systematically reviewed prospective studies that reported on acupuncture related AE. The protocol has been registered at the International prospective register of systematic reviews (PROSPERO) (23) on September 25, 2019 (registration number CRD42020151930; online supplementary appendix S1). The research checklist according to the

preferred reporting items for systematic reviews and meta-analyses (PRISMA) (24) and according to the guideline of Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (25) are displayed in the online supplementary appendix S2.

Search strategy

We searched Pubmed, Scopus, and EMBASE for articles published before September 15, 2019 by applying the following search strategy: 1: acupuncture; 2: “adverse event”; 3:”adverse events”; 4: “adverse effect”; 5: “adverse effects”; #1 AND #2; #1 AND #3; #1 AND #4; #1 AND #5. Additional records were identified from previous reviews on acupuncture related AE.(17) “Acupuncture” and “adverse effects” are MeSH terms.

In- and exclusion criteria

We included articles reporting on prospective studies (cohort studies, RCTs, surveys or surveillances) assessing AE associated with needle acupuncture involving manual or electrical stimulation combined with or without moxibustion in humans as their primary outcome. Case reports and case series were not included. Only articles published in English or German were included. Publications on assessments of acupuncture point injection therapies or non-penetrating acupuncture point stimulation such as laser acupuncture, acupressure or transcutaneous electrical nerve stimulation (TENS) were excluded. We also excluded articles reporting solely on moxibustion or restricted acupuncture regimens such as press-needle, auricular or one-point acupuncture. Trials focusing just on one type of acupuncture related AE or just on a narrowly defined patient population were excluded.

Article selection and data extraction

Article selection was performed independently by two reviewers (WZ and PB, TS and PB, or LM and PB). Retrieved records were first screened for eligibility by abstract. Full texts were obtained for the remaining articles. Final decision about eligibility was obtained by consensus of all four reviewers.

Estimates of overall risks and risks for each reported type of AE were extracted as absolute number of patients with AE per total number of patients and treatments with AE per total number of treatments. Data concerning AE from sham- or placebo-acupuncture treatments were not extracted. The different types of AE were assigned to one of the following categories: bleeding, local pain, other local AE, distant pain, central nervous system, peripheral nervous system, vegetative nervous system, motor system, gastrointestinal / gynaecological system, cardiovascular system, respiratory system, generalized skin reactions, headache, emotional interference, sleeping problems, AE related to moxibustion, needling malpractice, aggravation of symptoms, other or unclassified AE (online supplementary appendix S3).

Following the differentiation between AE and adverse drug reactions (ADR) defined by the International Conference on Harmonization (ICH) of Good Clinical Practice,(26) articles were classified into reports on adverse events irrespective of their causal relationship to acupuncture and adverse reactions for which a causal relationship was a reasonable possibility. Serious adverse events (SAE) were reported as indicated in the included articles as in accordance with the ICH-criteria. These include any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.(26) AE definitions and severity assessments as stated in the included publications are provided in the online supplementary appendix S4. Causality assessment of SAE was performed by independent acupuncture therapists who were medical doctors who received more than 300 hours of acupuncture training and with more than ten years of intensive acupuncture practice. As the basis of this assessment was limited to incomplete information provided in the articles lacking e.g. time references, the standard

categories of the WHO-UMC causality assessment system (27) were reduced to possibly or unlikely related to acupuncture or unclassifiable.

AE risk estimates given as patients with AE per total number of patients were interpreted according to the guidelines of the Council for International Organizations of Medical Sciences (CIOMS) as very common (≥ 1/10 patients), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000).(28)

Documentation of study characteristics included study type, country in which the study was conducted, reporter, method and time point of AE assessment, complaint as well as age and gender structure of the study population, average number and frequency of treatments per patient, average number of needles per treatment, needle in time, acupuncture style, and method of needle stimulation, as well as number, gender, training, and years of experience of acupuncturists. Data on patients' and acupuncturists' AE reports from the article published by Weidenhammer et al. in 2008 were handled as two separate trials.

Risk of bias assessment

Included studies were assessed for risk of bias according to a checklist developed by Faillie and colleagues for systematic reviews focusing on drug adverse events.(29) This checklist is applicable to RCTS, cohort studies, case-control studies, nested case-control studies, and systematic reviews. The questions are structured in 8 risk of bias domains. Possible answers are "Not applicable" (n/a), "Yes" (Y), "Unclear" (U), or "No" (N). A summary risk of bias assessment is provided for each domain as well as for the whole study. According to the inclusion criteria of this review, questions concerning systematic reviews, cross-over trials, and case-control studies were not applicable.

Data analysis

Data were analysed using the package meta implemented in R.(30) Pooled estimates with 95% confidence intervals (CI) for overall AE risk and risks of different types of AE were obtained from proportion meta-analyses. Random effects models were calculated by the Hartung-Knapp method with arcsine transformation of proportions. Cochran Q test, and I^2 statistics were used to assess the heterogeneity of included studies. Meta-analyses were performed for the overall risks for an AE, for SAE, for AE requiring treatment and the risks for the different types of AE given as the number of patients with AE per total number of patients undergoing an acupuncture series or as the number of treatments with AE per total number of treatments performed. All studies reporting the respective risks were included in the different meta-analyses. All AE that were reported separately in the articles, but that were allocated to the same AE category, were treated as they had occurred in different patients or treatments, respectively. Sensitivity analyses were performed for studies that explicitly only reported about AE that had, at the discretion of the assessors', a causal relationship to acupuncture treatments. None of the articles reported the mean and variance of the number of AE per treatment. Thus, the expected number of AE per treatment could not be estimated by meta-analysis but just by considering the sum of AE relative to the sum of treatments. An additional sensitivity analysis was performed by excluding AE that are usually very mild and transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point. AE of such type that were indicated by any means as significant were not excluded for this sensitivity analysis.

Patient and public involvement

No patients were involved in defining the research question, the outcome measures, the design or conduct of this review. No patients were asked to advise on interpretation of results. Authors will share the results during patient seminars and information events. A concise version of the results will be made available for non-profit acupuncture organisations to be presented on their webpages.

Results

Study characteristics

7677 records were retrieved from the database search and two were identified from previous reviews on acupuncture related adverse events. 7499 records could be screened by abstract and for 180 articles full-texts were obtained. A total of 22 articles reporting on 21 studies covering 12.9 million treatments met our inclusion criteria (Figure 1).(31-52) In two studies different data assessments on different subpopulations were performed and are treated independently in the present analyses. In one study patient reported AE were assessed after one of the first treatments and three months after treatment,(38, 39) and in one large study AE were documented by therapists and in addition by a subgroup of patients.(46)

Study characteristics are provided in table 1. The four largest trials with one to five hundred thousand patients treated in over 750 thousand acupuncture sessions were cohort studies performed as part of the German Model Projects on Acupuncture (*Modellvorhaben Akupunktur*).(33, 41, 46, 49) Three nationwide surveys from the UK (described in four articles),(38-40, 48) one in-house surveillance report from Japan (51) and one summary of AE assessments nested within three Chinese RCTs (52) included two to six thousand patients receiving over 30 thousand treatments, respectively. In three surveys, two from South-Korea,(44, 45) one from Japan, (35) and one from Brazil,(32) around one to two thousand patients were included and treated in up to 14 thousand acupuncture sessions. One nationwide survey conducted in Sweden reported on the risk of AE based on data from over nine thousand acupuncture sessions.(43) In seven studies less than 500 patients receiving maximum 3.5 thousand treatments were included; four AE assessments nested within RCTS or clinical trials from China,(36, 47) Hong-Kong,(31) and Sweden,(37) one Japanese (50) and one German survey (34) as well as one German cohort study.(42) In most studies acupuncture was used to treat pain in middle aged patients. In six articles no details on the patients' condition were provided.(34, 35, 40, 43, 48, 50) Two articles reported explicitly on short-term AE after one particular treatment only.(39, 45) All but five articles provided sufficient information to infer that acupuncturists had a firm medical background and / or had received intensive acupuncture training.(34, 36, 37, 42, 43) One German survey also included "other practitioners" most likely non-medical practitioners (*Heilpraktiker*) with non-standardized acupuncture training.(34)

Eight articles described AE reported by patients only (31, 32, 37-39, 45, 46, 49) and seven articles AE reported by acupuncturists only.(33, 40, 41, 44, 46, 48, 51) As before said Weidenhammer et al. described therapists' and patients' reports on AE separately.(46) Zhao et al. combined the AE reports from patients and acupuncturists.(52) In five articles it was explicitly stated that acupuncturists recording the AE also queried their patients about any uncomfortable experience during or after treatment.(34-36, 43, 50) In two trials AE were documented by an independent assessor.(42, 47) In eight of the 22 included articles AE were reported irrespective of their relationship to acupuncture,(31, 33, 34, 37, 40, 48, 51, 52) while descriptions of AE assessments in twelve articles suggest that only AE related to the acupuncture treatment were documented,(32, 35, 36, 38, 39, 42-44, 46, 49, 50) and one article did not provide information about the AE definition.(45) Further discrepancies were found in definitions of certain reactions as therapeutically intended. For example, da Silva et al. did not count aggravation of symptoms as AE, because of difficulties in determining causality as well as severity and because of common notion among practitioners that transient worsening forms part of the acupuncture treatment.(32) In contrast White et al. reported observations of aggravated symptoms as AE, but only those that were not followed by substantial improvements.(48) In contrast, the other articles did not specify aggravation of symptoms further.(33-35, 37, 38, 42, 46, 49, 50) In addition, Endres et al. did report on erythema at the needling site (which was accounted for in the present analysis), but did not include it in their overall AE incidence report, as this can also be regarded as desired acupuncture reaction.(33)

1st Author year	Country	Study type	Patients			Treatments				Acupuncturists				AE assessment		
			n total (female)	Age [a]	Indication	n (total)	n / patient	n needles	Stimulation	n total (n female)	Medical background	Acupuncture training	Acupuncture practice	Reporter	Tool	Time point
Chung 2015	Hong-Kong	RCT	59 (46)*)	49 ± 10*)	Insomnia in major depressive disorder	531	9 / 3 w	14	EA	n.i.	TCM doctors	n.i.	> 3 a	P	SL & OQ any AE	after 3rd, 6th, 9th treatment
da Silva 2014	Brazil	Cohort monocentric	1157 (n.i.)	n.i.	Musculoskeletal, emotional &respiratory disorders i.a.	13,884	12#)	n.i.	MA	n.i.	MD	in training	n.i.	P	SL & OQ AE related to acu.	after each treatment
Endres 2004	Germany	Cohort nationwide private clinics	190,924 (130,974)	f: 58 ± 16 m: 55 ± 15	Chronic headache, LBP or arthrosis (> 6 m)	1.77 M	apx. 10 / 4 - 8 w	n.i.	n.i.	12,000 (n.i.)	MD	> 140 h	n.i.	A	SL & OQ any AE	after last treatment
Ernst 2003	Germany	Survey private practices	409 (279)	n.i.	n.i.	3,535	f: 9.0 m: 7.9	n.i.	n.i.	29 (n.i.)	MD & other practitioners	n.i.	n.i.	A also asking P	SL & OQ any AE	after each treatment; at subsequent visit
Furuse 2017	Japan	Survey 8 acupuncture clinics	2180 (1288)	54 ± 19	n.i.	14,039	6.4#	n.i.	MA, EA & Moxa	232 (93)	Japanese lic. acupuncturists	> 3 a	9 ± 10 a	A also asking P	SL AE related to acu.	after each treatment; at subsequent visit
Leung 2009	Hong-Kong	11 clinical trials (not specified)	254 (n.i.)	n.i.	Chronic pain, neurological & urological conditions	2,000	n.i.	5 avg.	MA & EA	2 (n.i.)	TCM doctors	n.i.	n.i.	A also asking P	SL AE related to acu.	after each treatment & subsequent visit
List 1992	Sweden	RCT monocentric	29 (n.i.)	median 40**)	Craniomandibular disorder	apx. 174	≥ 6 / 6 - 8 w	12 avg.	MA & EA	1 (0)	n.i.	n.i.	n.i.	P	SL & OQ any AE	after last treatment
MacPherson 2001	UK	Survey nationwide private practices	n.i.	n.i.	n.i.	34,407	n.i.	1 - 20	n.i.	574 (374)	MD & physio-therapists	1 – 2 a 11% ≥ 3 a 89%	< 10 a apx. 60% ≥ 10 a apx. 40%	A	SL & OQ any AE	upon recognition
MacPherson 2004 A	UK	Survey nationwide private practices	6,348 (4,821)	52 ± 15	Musculoskeletal, psychological, general, neurological, gyne-cological, obstetric & respiratory conditions; wellbeing	30,196	4.8	n.i.	MA & EA	638 (406)	MD & physio-therapists	> 3 a	< 10 a 58% ≥ 10 a 42%	P	SL & OQ AE related to acu.	3 m after inclusion
MacPherson 2005 A			9,408 (6,961)	51		9,408	1								SL imm. AE AE related to acu.	After the 1st / one of the 1st treatments
Melchart 1998	Germany	Cohort monocentric	121 (88)	54 ± 13	Mainly chronic pain	apx. 1,200	9.9 ± 4.7	n.i.	n.i.	n.i.	TCM doctors	n.i.	n.i.	Independent A asking P	SL & FT AE related to acu.	at subsequent visit
Melchart 2004	Germany	Cohort nationwide private clinics	97,733 (78,675)	55 ± 16	Chronic headache, osteoarthritis, LBP	apx. 760,000	7.8 ± 2.4	12.6 ± 5.1	n.i.	7050 (n.i.)	MD	> 140 h (19% > 350 h)	n.i.	A	SL & FT AE related to acu.	after last treatment
Odsberg 2001	Sweden	Survey private practices	n.i.	n.i.	n.i.	9,277	n.i.	n.i.	MA & EA	187 (n.i.)	Physio-therapists	n.i.	n.i.	A also asking P	n.i. AE related to acu.	after each treatment
Park 2009	South-Korea	Survey two-centred	1,095 (696)	58 ± 13	Stroke, headache, hyper-tension, dizziness, i.a.	1,095	1	n.i.	n.i.	8 (n.i.)	Korean medicine doctor	n.i.	>10a	P	n.i.	after 1 arbitrary treatment
Park 2010	South-Korea	Survey private practices	2,226 (n.i.)	n.i.	n.i. (patients with AE mainly pain conditions)	3,071	1.4 / ≤ 5 w#)	n.i.	n.i.	13 (n.i.)	Oriental medicine.	6 a	< 3a 70% ≥ 3a 30%	A	SL AE related to acu.	upon recognition
Weiden-hammer 2008 B	Germany	Cohort nationwide private clinics	503,397 (40,5235)	54 ± 16	Chronic headache, LBP, osteoarthrosis (> 6 m)	4.2 M	8.4 (2.9)	n.i.	n.i.	9918 (3570)	MD	140 h (22% > 350 h)	n.i.	A	SL & FT AE related to acu.	after last treatment
			882847 (n.i.)	n.i.		7.9 M	n.i.								OQ - SAE only AE related to acu.	upon recognition
			5,998 (5,072)	55 ± 15		apx. 51582#)	8.6 (3.0)			9429 (n.i.)				P	OQ AE related to acu.	after last treatment
Wen 2016	China	RCT monocentric	120 (84)	59 ± 7	Posterior circulation ischemia	1,680	14 / 3 - 4 w	≤ 9	MA	1 (n.i.)	n.i.	n.i.	> 20 a	Blinded assessor	n.i. AE related to acu.	after each treatment
White 2001	UK	Survey private practices	n.i.	n.i.	n.i.	31,822	n.i.	n.i.	n.i.	78 (29)***)	MD & physio-therapists	≤ 100 h 43% > 100 h 57%	≤ 10 a 65% > 10 a 35%	A	SL & OQ any AE	upon recognition
Witt 2009	Germany	Cohort nationwide private clinics	229,230 (148,541)	51 ± 14	Chronic headache, osteo-arthritis, LBP, all. rhinitis, asthma, dysmenorrhea	2.2 M	10.2 ± 3.0	n.i.	n.i.	13579 (5418)	MD	> 140 h (15% > 350h)	6.9 ± 5.3 a	P	OQ AE related to acu.	after last treatment
Yamashita 1999	Japan	In-house surveillance	5,008 (2,804)	Mostly 40 - 50 a	Musculoskeletal disorder, miscellaneous complaints	65,482	13 avg.	n.i.	MA, EA & Moxa	84 (n.i.)	Japanese lic. acupuncturists	> 3 a	< 1 a 64% ≥ 1 a 36%	A	OQ any AE	upon recognition
Yamashita 2000	Japan	Survey monocentric	391 (n.i.)	12 - 88	n.i.	1,441	3.7#)	21#)	MA & EA	7 (n.i.)	Japanese lic. acupuncturists	> 3 a	n.i.	A also asking P	OQ AE related to acu.	after each treatment; at subsequent visit
Zhao 2011	China	3 RCTs multicenter	1,968 (1,239)	39 ± 14	Migraine, dyspepsia, Bell's palsy	39,360	20 / 4 w	2 - 5	MA & EA	n.i.	TCM doctors	≥ 8 a	> 10 a	P & A	SL & OQ any AE	after each treatment & after last treatment

Table 1: Study characteristics

AE: adverse event; SAE: serious adverse event; acu: acupuncture; MA: manual acupuncture; EA: electroacupuncture; Moxa: moxibustion; m: male, f: female; LBP: low back pain; MD: medical doctors; lic.: licensed; TCM: Traditional Chinese Medicine; SL: selection list; OQ: open questions, FT: free text; P: patients; A: acupuncturists; imm.: immediate; X ± X: mean ± standard deviation; a: year; w: weeks; h: hours; M: million; avg.: on average; i.a. inter alia; apx.: approximately; n.i.: not indicated; A) overlapping study populations from the same survey B) reports of patients and therapists separately presented; *) including one drop out prior to treatment; **) refers to total study population (n=61); ***) further professional details only provided by 59 acupuncturists; #) approximation based on other reported data

Risk of bias assessment

According to the inclusion criteria the study objective was clearly described in all articles (Figure 2, category A). Study design was clear for all but one article, which stated that data were collected in the course of 11 clinical trials without further specification.(36) Also, all but one AE assessment were free of a run in period. In one RCT the safety assessment was initiated with a short delay.(37) Both irregularities were rated as unlikely to introduce bias into AE documentation. High risk for selection bias (Figure 2, category B) was identified for the four RCTs and the AE assessment in 11 clinical trials (23% of articles), due to exclusion of patients with comorbidities or bleeding tendency. In contrast, in all surveys and cohort studies (77%) the risk for selection bias was rated as unclear due to an indistinct selection of therapists and / or patients, inclusion of voluntarily participating acupuncturists or acupuncturists from specialized medical centres only. Furthermore, none of the articles stated that patients were naive to acupuncture. Risk of bias due to study withdrawal or drop-out (Figure 2, category C) was rated as low for all RCTs and two surveys, that only reported on short-term AE (27%), (39, 45) and as high for one survey (5%), because treatment was ceased for 40% of patients with AE.(44) For the remaining studies (68%) the risk of bias due to early treatment termination was rated as unclear, as withdrawals and drop-outs due to AE were not reported. The risk of information bias regarding the safety outcome (Figure 2, category D) was rated as high for one study (5%) because of an exclusive documentation of repeatedly occurring AE (37) and as unclear for all remaining studies (95%). At this, AE reporting by patients or acupuncturists instead of an independent assessor was classified as an unclear risk for social desirability bias. Using only a selection list (35, 36, 39, 44) or only open questions as AE assessment tool,(49-51), lack of reporting on the AE assessment tool (43, 45, 47) or the definition of the safety outcome, and selection of the time-point of the AE assessment (only directly after treatment,(32, 33, 43, 47) only after the last treatment initiation,(37, 38, 41, 46, 49) solely upon recognition (40, 44, 48, 51)) were rated as possible but unclear sources of detection bias. Further risk of information bias (Figure 2, category E) appeared to be unclear due to poor reporting of treatment details in all but seven studies (32%).(31, 37, 40, 41, 47, 50, 52) Bias arising from differential care, confounder assessment and statistical methods to control for confounding (Figure 2, category F) was rated as low, as crude AE risk estimates and not relative risks with respect to a comparator group were extracted. The risk of bias due to other statistical methods (Figure 2, category G) was also rated as low, as reporting of AE incidence was clear and well-structured in all articles.

Bias due to conflict of interest (Figure 2, category H) might be present in four articles (18%) due to funding by institution with direct interest in the public acknowledgement of acupuncture.(38, 39, 43, 44) In eight articles (36%) funding or other conflicts of interest were not described.(34, 36, 37, 40, 42, 48, 50, 51) The ten remaining articles (45%) included an explicit statement about funding by independent institutions and absence of other conflicts of interest. For all studies the overall risk of bias was rated as unclear based on the large proportion of unclear sources of bias.

Overall risk of acupuncture related adverse events

Eleven studies including 845,637 patients that assessed the overall AE risk as patients with AE among the total number of patients undergoing an acupuncture series were combined in a meta-analysis. The overall risk for at least one AE during a series of acupuncture treatments was estimated to be 9.31 (95%-CI 5.10 to 14.62) per 100 patients treated (Figure 3A). (31, 34, 36, 38, 41, 42, 46, 47, 49, 52) The median number of treatments per patient was 9 (min 4.8; max 14), and the total number of treatments exceeded 7.4 million. Visual inspection neither indicated an association of the incidence of AE with the number of treatments per acupuncture series nor with the study type (online supplementary appendix S5). Five studies reported the total number of acupuncture treatments with AE relative to the total number of treatments performed.(32, 34, 36, 40, 42) Meta-analysis of these studies covering 55,026 treatments in total

resulted in a risk of 7.57 (95%-CI 1.43 to 17.95) treatments with AE per 100 treatments (Figure 3B). Sensitivity analysis of studies reporting on adverse acupuncture reactions and not on AE irrespective of their relationship to acupuncture treatments resulted in similar estimates (32, 36, 38, 40, 41, 46, 47, 49); 8.23 (95%-CI 6.42 to 10.25) patients with at least one AE out of 100 patients (Figure 3C) and 6.08 (95%-CI 0.00 to 38.76) treatment with AE out of 100 treatments (Figure 3D). Heterogeneity for all meta-analyses mentioned above (including the sensitivity analyses) was substantial as indicated by an I^2 between 98% and 100% ($p < 0.01$).

Thirteen articles reported the incidences of different types of AE per treatment (table 2).(32, 34-36, 39, 40, 42-45, 48, 50, 51) The average number of AE per 100 treatments varied between 0.14 and 69.12. In total 18,002 AE were reported in of 190,661 treatments, which makes on average 9.44 AE per 100 treatments. Exclusion of AE that are usually mild and transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point, reduced this number to 4.81 (min - max 0.10 – 36.92) AE per 100 treatments.

Study	Number of treatments	Number of AE		AE incidence per 100 treatments		Bleeding, pain, flare at needling site as % of all AE
		total	excluding bleeding, pain & flare	total	excluding bleeding, pain & flare	
Park 2009	1095	193	64	17.63	5.84	66.84%
Ernst 2003	3535	632	403	17.88	11.40	36.23%
Melchart 1998	1200	120	66	10.00	5.50	45.00%
Yamashita 1999	65482	94	67	0.14	0.10	28.72%
Yamashita 2000	1441	996	114	69.12	7.91	88.55%
MacPherson 2001	34407	4544	3406	13.21	9.90	25.04%
Odsberg 2001	9277	2108	390	22.72	4.20	81.50%
White 2001	31822	2176	820	6.84	2.58	62.32%
MacPherson 2005	9408	5071	3473	53.90	36.92	31.51%
Leung 2009	2000	8	0	0.40	0.00	100.00%
Park 2010	3071	99	26	3.22	0.85	73.74%
da Silva 2014	13884	1107	117	7.97	0.84	89.43%
Furuse 2017	14039	854	232	6.08	1.65	72.83%
Overall	190661	18002	9178	9.44	4.81	49.02%

Table 2: Number of adverse events (AE) per treatment

Serious acupuncture related adverse events

SAE were observed in five studies including 1,182,860 patients undergoing 10,570,678 treatments with incidences between two and 40 SAE in 100,000 patients undergoing a treatment series and between two and 99 in one million treatments, respectively.(33, 38, 41, 46, 51) Four articles reported that none of the AE observed in a total of 1,922 patients undergoing 19,005 treatments required medical treatment,(32, 36, 47, 50) and authors of five articles concluded that none of the AE observed in 122,699 treatments fulfilled the ICH-criteria for SAE.(35, 40, 44, 48, 52) Eight articles did not mention SAE or any AE description that allowed for inferences on SAE.(31, 34, 37, 39, 42, 43, 45, 49)

Meta-analyses of the overall risk for a SAE resulted in 1.01 (95%-CI 0.23 to 2.33) patients with SAE in 10,000 patients undergoing an acupuncture series (Figure 4A, 11 studies 1,188,930 patients) and 7.98 (95%-CI 1.39 to 20.00) SAE in one million treatments (Figure 4B, 14 studies 10,712,382 treatments). Exclusion of studies with zero SAE incidences

changed these estimates to 1.47 (95%-CI 0.10 to 4.46) in 10,000 patients suffering from a SAE when undergoing an acupuncture series and 16.90 (95%-CI 0.49 to 56.60) in one million treatments causing an SAE. Sensitivity analyses of studies that only reported reactions with a plausible relationship to acupuncture resulted in risk estimates of 0.45 (95%-CI 0.06. to 1.18) SAE per 10,000 patients (Figure 4C) and 5.45 (95%-CI 0.50 to 15.67) per one million treatments (Figure 4D). Again, heterogeneity between studies included in these two meta-analyses was substantial ($I^2 > 85\%$, $p < 0.001$).

The causality assessment of the 73 SAE conducted by two acupuncture experts (table 3) resulted in 32 SAE (44%) being possibly related to acupuncture. Among those, pneumothorax, strong cardiovascular or vasovagal reactions, and fall or trauma were the most frequent SAE with a frequency of 1 to 3 cases in one million treatments each. One article that was not taken into account in the SAE meta-analyses as observed AE were not categorized in minor AE and SAE also reported two cases of pneumothorax in over 200,000 patients receiving on average 10 acupuncture treatments.(49) One of the included trials documented deaths occurring in the study population. Nineteen SAE (26%) were rate as unlikely related to acupuncture. Among those were nine deaths observed in one study in patients of an age between 67 and 87 years and related to a pre-existing health conditions.(33) Authors reported that the resulting death rate of 4.71 per 100,000 patients is below the expected death rate derived from population statistics. Other SAE classified as unlikely related to acupuncture were a circulatory reaction with amnesia, suicidal tendencies, acute general infection, a car crash two days after treatment, a malignant parotid tumour, tonic-clonic seizures, and an ophistotonus. Twenty-two SAE (30%), intervertebral disk prolapses and hospitalizations due to pain exacerbation or unknown reasons, were rated as “unclassifiable”.

Endres 2004	**Causality**	**n**
- Death	unlikely	9
- Fall or trauma, with or without fracture	possible	4
- Acute general infection with hospitalization	unlikely	2
- Allergic reaction to concomitant medication (atopy)	possible	1
- Stroke with hospitalization	unlikely	3
- Cardiovascular problems (hospital admission)	possible	3
- Intervertebral disk prolapse, pain exacerbation with hospital admission	unclassifiable	5
- Malignant parotid tumor (hospital admission)	unlikely	1
- Hospitalization (unknown reasons)	unclassifiable	17

Melchart 2004	**Causality**	**n**
- Exacerbation of depression	possible	1
- Hypertensive crisis	possible	1
- Vasovagal reaction	possible	1
- Asthma attack with hypertension and angina	possible	1
- Pneumothorax	possible	2

Yamashita 1999	**Causality**	**n**
- Hospitalization of patient with asthma because of coughing	possible	1
- 1 case of deep burn that recovered after 2 years	possible	1

Weidenhammer 2008 ther.	**Causality**	**n**
- Pneumothorax	possible	5
- Suicidiation in a patient with borderline syndrome	unlikely	1
- Hypertensive crisis	possible	1
- Syncope (vasovagal reaction)	possible	2
- Asthma attack in a patient with asthma	possible	1
- Erysipelas (one in a patient with lymphedema)	possible	2
- Circulatory collapse (one with uncontrolled defecation and one with vertigo and paresthesia)	possible	2
- Circulatory reaction with amnesia	unlikely	1
- Tonic-clonic seizures and ophistotonus	unlikely	1
- Infection of the knee joint with E. coli bacteria	possible	1

MacPherson 2004	**Causality**	**n**
- Low back pain in breast cancer patient, hospital admission, disappeared without medication, since then no more LBP	possible	1
- Car crash 2d after acupuncture, very little sleep the night before	unlikely	1
- Skin rash and feeling ill for several weeks accompanied by decrease of ME symptoms and feeling of catharsis (no treatment)	possible	1

Table 3: Causality assessment of serious adverse events as reported in included articles

The total number of serious adverse events (SAE) as well as the total number of treatments in each study can be identified from figure 4.

Acupuncture related adverse events requiring treatment

Eight studies determining the number of patients with AE requiring treatment during an acupuncture series included 1,211,791 patients. The meta-analysis of these studies yielded a summary estimate of 1.14 (95%-CI 0.00 to 7.37) in 1000 patients for the risk to suffer from an AE that required treatment when undergoing an acupuncture series (Figure 5). (31, 32, 36, 41, 46, 47, 49, 50) Also here, heterogeneity was substantial (I^2 100%). Two articles, that had defined required treatment as an SAE criterion, reported lower incidences (2 and 6 events per 100,000 patients) (41, 46) than other two articles, reporting on AE requiring treatment without referring to SAE (1.7 and 2.2 in 100 patients).(31, 49)

Risk of different types of minor adverse events

Overall risk for the different types of minor AE (categorization see online supplementary appendix S3) were estimated in separated meta-analyses as patients with AE per total number of patients undergoing a treatment series or as treatments with AE per total number of treatments (Table 4). Risks estimated in single studies (online supplementary appendix S6 and S7) varied largely for all types of minor AE. Most frequent and commonly occurring minor AE with summary risk estimated between one and five percent of patients undergoing an acupuncture series were bleeding events, pain at the needling site, other local AE, vegetative reactions, aggravation of symptoms, and events related to the central nervous system. Summary risk estimates for bleeding events, needle site pain, vegetative reactions, and aggravation of symptoms also ranged from 1% to 5% of treatments, while meta-analysis of symptoms related to the central nervous system per acupuncture treatment resulted in a risk of two in 1000 treatments. AE estimated to be uncommon with summary risk estimates of one to seven out of 1000 patients undergoing an acupuncture series were symptoms of the peripheral nervous system, pain distant to the needling site, gastrointestinal or gynaecological symptoms, headache, cardiovascular symptoms, affection of the motor system, generalized skin reactions, adverse emotional reactions, and sleeping problems. Symptoms affecting the peripheral nervous system, distant pain, as well as gastrointestinal or gynaecological symptoms were estimated to occur in one to seven out of 1000 treatments; headache, cardiovascular, and motor symptoms as well as adverse emotional reactions only in one to eight out of 10,000 treatments. The risk for respiratory AE was estimated to be rare with a summary risk estimate of four out of 10,000 patients undergoing an acupuncture series and three out of 10,000 treatments. Summary risk estimates for AE caused by therapists' malpractice and burns caused by moxibustion were between one and two in 1000 patients undergoing an acupuncture series and between two in 10,000 to one in 1000 treatments, respectively.

Some of the studies showed outlying incidences for particular types of minor AE. List et al. observed at least one vegetative reaction in the course of an acupuncture series for craniomandibular disorder in over half of the patients (58.6%),(37) and MacPherson et al. reported vegetative reactions after over a quarter of treatments (27.9%).(39) These findings exceed the frequency of vegetative reactions of up to 13.6% of patients identified in the remaining studies and was mainly based on patient reports of abnormal tiredness after treatment. List et al. also report the highest incidence of aggravation of symptoms with 93% of CMD patients as well as the highest frequency of needle site pain with 44.8 % of patients. This was followed by an RCT with 32.2% of patients suffering needle site pain (31) and a cohort study among chronic pain patients of which 10% suffered aggravation of symptoms after receiving acupuncture.(42) The remaining 19 articles reported incidences smaller than 3% for aggravation of symptoms and 14% for needle site pain.

Type of AE	Number of studies	Sum of patients	Risk as patients with AE per 100 patients [95%-CI] overall	min	max	Tau² I²	Number of studies	Sum of treatments	Risk as treatments with AE per 100 treatments [95%-CI] overall	min	max	Tau² I²
Bleeding	13	1038741	4.67 [2.08; 8.22]	0.48 [0.32; 0.67]	25.18 [21.10; 29.50]	0.0008 99.4%**	13	190661	4.92 [1.18; 11.01]	0.03 [0.02; 0.05]	45.45 [42.89; 48.03]	0.0169 99.9%**
Needle site pain	14	1038907	3.75 [0.74; 8.94]	0.05 [0.04; 0.06]	44.83 [27.46; 62.87]	0.0085 99.9%**	12	188661	2.43 [0.63; 5.35]	0.01 [0.00; 0.02]	15.75 [13.92; 17.68]	0.0095 99.8%**
Other local AE	10	1034610	2.79 [0.02; 10.01]	0.15 [0.14; 0.16]	35.59 [23.97; 48.14]	0.0494 100.0%*	11	187566	0.13 [0.04; 0.27]	0.00 [0.00; 0.01]	0.90 [0.48; 1.46]	0.0004 96.4%**
Vegetative reaction	12	1036607	1.95 [0.40; 4.63]	0.08 [0.07; 0.08]	58.62 [40.52; 75.59]	0.0012 99.7%**	12	188661	2.24 [0.21; 6.35]	0.00 [0.00; 0.01]	27.87 [26.97; 28.78]	0.0213 99.9%**
Aggravation of symptoms	11	1036760	1.48 [0.00; 5.90]	0.08 [0.07; 0.09]	93.10 [81.26; 99.30]	0.0017 99.8%**	10	173682	0.84 [0.26; 1.75]	0.00 [0.00; 0.01]	2.83 [2.66; 3.01]	0.0055 99.7%**
Central nervous system	9	244553	1.45 [0.07; 4.51]	0.05 [0.00; 0.20]	37.93 [21.45; 55.99]	0.0018 96.3%**	11	179253	0.20 [0.05; 0.46]	0.01 [0.00; 0.02]	1.08 [0.76; 1.44]	0.0011 98.4%**
Peripheral nervous system	8	433118	0.69 [0.02; 2.34]	0.08 [0.07; 0.10]	27.59 [13.14; 44.96]	0.0004 98.1%**	10	152813	0.19 [0.02; 0.55]	0.00 [0.00; 0.01]	1.46 [0.84; 2.26]	0.0008 98.0%**
Distant pain	5	241817	0.60 [0.21; 1.20]	0.17 [0.09; 0.29]	0.95 [0.72; 1.21]	0.0005 92.6%**	4	46456	0.73 [0.00; 5.02]	0.07 [0.00; 0.27]	4.49 [4.08; 4.91]	0.0085 99.5%**
Gastrointestinal / gynaecologcial system	9	747559	0.60 [0.04; 1.81]	0.01 [0.01; 0.02]	17.24 [5.94; 32.83]	0.0008 99.3%**	10	186125	0.15 [0.03; 0.38]	0.01 [0.00; 0.02]	1.18 [0.97; 1.41]	0.0008 98.2%**
Unclassified AE	10	1036307	0.57 [0.01; 1.95]	0.07 [0.05; 0.08]	17.85 [14.29; 21.70]	0.0003 99.0%**	9	172136	0.47 [0.03; 1.46]	0.00 [0.00; 0.01]	5.46 [4.74; 6.23]	0.0025 99.4%**
Headache	9	845745	0.51 [0.03; 1.55]	0.03 [0.03; 0.04]	13.56 [6.10; 23.38]	0.0012 99.6%**	7	97592	0.04 [0.01; 0.10]	0.00 [0.00; 0.01]	0.14 [0.01; 0.40]	0.0002 90.3%**
Cardiovascular system	5	739155	0.40 [0.24; 0.61]	0.27 [0.25; 0.29]	0.83 [0.00; 3.21]	0.0001 96.4%**	3	18774	0.03 [0.00; 0.13]	0.01 [0.00; 0.04]	0.08 [0.00; 0.33]	0.0001 21.2%
Motor system	5	237634	0.38 [0.00; 4.79]	0.08 [0.07; 0.09]	41.38 [24.41; 59.48]	0.0011 94.6%**	5	82112	0.01 [0.00; 0.04]	0.00 [0.00; 0.01]	0.03 [0.00; 0.11]	0.0001 58.1%*
Generalized skin reaction	2	229289	0.35 [0.00; 35.67]	0.09 [0.08; 0.10]	1.69 [0.00; 6.52]	0.0029 58.2%	-					
Needling malpractice	7	1029871	0.22 [0.01; 0.67]	0.00 [0.00; 0.00]	1.04 [0.81; 1.30]	0.0009 99.7%**	7	164146	0.12 [0.02; 0.28]	0.01 [0.00; 0.02]	0.62 [0.28; 1.10]	0.0002 95.1%**
Emotional interference	6	930429	0.20 [0.00; 0.81]	0.02 [0.02; 0.02]	1.24 [0.99; 1.53]	0.0002 98.7%**	7	155131	0.08 [0.00; 0.27]	0.01 [0.00; 0.02]	0.67 [0.51; 0.84]	0.0004 96.8%**
Sleeping problems	5	432529	0.16 [0.00; 0.91]	0.04 [0.03; 0.05]	20.69 [8.19; 37.03]	0.0001 97.1%**	-					
AE caused by moxibustion	4	428682	0.14 [0.00; 1.16]	0.00 [0.00; 0.00]	0.96 [0.60; 1.42]	0.0002 98.3%**	4	145750	0.02 [0.00; 0.18]	0.00 [0.00; 0.01]	0.17 [0.11; 0.25]	0.0001 95.0%**
Respiratory system	3	235637	0.04 [0.00; 0.26]	0.02 [0.01; 0.02]	0.24 [0.00; 0.96]	0.0001 69.0%*	1	3535	0.03 [0.00; 0.11]			

Table 4: Summary risk estimated for different types of adverse events

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses; min: minimum; max: maximum; 95%-CI: 95% confidence interval *: p-value of Q-test for heterogeneity < 0.05; **: p-value of Q-test < 0.00

Discussion

Overall risk for acupuncture related adverse events

To date this is the first systematic review on prospective studies that provides summary risk estimates for acupuncture related adverse events derived from meta-analyses. The obtained results suggest that AE can be expected in every tenth patient that undergoes a series of acupuncture treatments and, overall, in every 13th treatment. Minor AE were common and represented the large majority of reported AE. About half of the reported minor AE are usually mild and transient or might even be regarded as part of the acupuncture treatment or therapeutically intended reactions (bleeding, needle site pain, flare around the needle site).(21) SAE can be expected rarely in about every 10,000th patient in the course of an acupuncture series and, overall, in every 125,000th treatment. Sensitivity analyses excluding studies with zero SAE incidences still suggest SAE being rare (every 7000th patient and every 60,000th treatment) particularly in comparison to SAE risk associated with pharmacological treatments.(16, 53, 54) AE requiring treatment occur uncommonly in about every 900th treatment, but additional AE are likely to also have involved medical decision-making about further diagnostics and follow-up. With meta-analyses for the overall risk of acupuncture related AE covering over 845,637 patients undergoing more than 7.4 million treatments and for the risk of SAE covering more than 1.2 million patients and 10.6 million treatments, the amount of data is equivalent to such available on the safety of e.g. common analgesics.(55, 56) This work augments insights on acupuncture related adverse events from previous reviews with either narrow eligibility criteria or focussing on case reports.(17) It includes data from the largest and most rigorous trials on acupuncture safety e.g. from the large nationwide cohort studies conducted in the UK and Germany which had not yet been aggregated.(33, 38-41, 46, 48, 49) Thus, our results provide rigorous support for the previously drawn conclusion (22, 57, 58) that acupuncture is among the safe treatments in medicine with SAE occurring rarely and half of the common minor AE being mild and transient. The uncommon AE requiring treatment necessitate solid medical competence of acupuncturists.

Types of adverse events related to acupuncture and implications for medical education of acupuncturists

Common minor AE were bleeding, needle site pain, other local reactions at the needling site, vegetative reactions, aggravation of symptoms, and AE related to the central nervous system (one to five out of 100 patients). This is in line with other reviews (22, 59) also on auricular (60) and paediatric acupuncture.(58) All other types of minor AE can be regarded as uncommon (1 to 7 out of 1000 patients), despite respiratory reactions that occurred very rarely (4 out of 10,000 patients). SAE most often reported were pneumothorax, strong cardiovascular or vasovagal reactions, and fall or trauma with one to three cases in one million treatments. Several other sometimes fatal SAE repeatedly described in case reports were not observed in the included studies; e.g. traumatic injuries of inner organs, local and systemic infections, subarachnoid bleeding, infective endocarditis, and cardiac tamponade.(61-65) This is likely due to the fact that acupuncturists in most of the studies were well trained, as SAE are claimed to be avoidable by proper acupuncture training and practice. Concordantly, cases of acupuncture malpractice were uncommon in the included trials.

Heterogeneity between studies

Possible causes of the substantial heterogeneity observed in all meta-analyses are differences in patient populations, needling regimens, AE definition, and AE assessment. Sensitivity analyses of trials reporting on adverse reactions with a plausible relationship to acupuncture resulted in only marginally lower overall AE risk estimates, but in a 50% lower SAE risk per patient and a 30% lower SAE risk per treatment. Reporting of SAE irrespective of the relationship to acupuncture is surely more conservative but likely to cause risk overestimation. In line with this, the causality of more than half of the SAE was rated as unlikely or unclassifiable by two independent acupuncture experts.

The variety of combinations of further patient treatment and assessment related factors prevented meaningful subgrouping of studies for additional sensitivity analyses, and the likeliness of their contribution to the observed heterogeneity makes formal assessment for publication bias unadvisable.(66) However, some distinct observations are worth to be discussed. Certain patient populations might be at higher risk to experience acupuncture related AE; e.g. in one study conducted among CMD patients AE were prominently frequent.(37) The role of acupuncture regimens in explaining heterogeneity could not be determined due to the limited information about number, location, and stimulation of needles. In contrast, the number of treatments per acupuncture series and study type seemed not to have impacted reported AE incidences.

A further possible cause of heterogeneity are differences in contrasting AE from therapeutically intended reactions that form part of acupuncture treatment; e.g. in contrast to international consensus, (18) aggravated symptoms were not or only in part counted as AE in two studies. (32, 48) Local reactions such as bleeding, pain, and flare at the needling site that represented half of the AE reported and are referred to as beneficial signs in standard acupuncture textbooks and by authors themselves.(20, 33) As the principle of acupuncture is to induce endogenous anti-nociceptive mechanisms and anti-inflammatory humoral responses through micro-trauma of skin and tissue, it can be argued that moderate local reactions are indeed desired reactions indicating an induction of regulative processes. Mild pain and a flare at the needling site have been linked to important neurophysiological mechanisms of acupuncture.(21) Additionally, aching or soreness at the needling site might be part of the intended deqi sensation (propagated sensation along the channels) supposedly related to acupuncture effectiveness.(19) The loss of small drops of blood upon needle withdrawal is interpreted as a sign for the patient's constitution called "excess" or "excess heat" in TCM terminology and was suggested not to be interpreted as AE.(67) On the other hand, standard text books explicitly explain needling techniques avoiding pain and bleeding.(20, 68) This debate calls for a uniform internationally recognized consensus on the definition of local acupuncture reactions as AE e.g. according to their quality and intensity.

In addition, included studies differed in reporters (acupuncturists, patients, acupuncturists also questioning patients, and independent assessors), the type of documentation (selection list, open questions, or a combination of both), and assessment time points. Due to the large variability of combinations the individual impact of these factors could not be estimated, but literature suggests that patients report more AE than therapists,(69) and that open questions presented to patients lead to lower risk estimates than the presentation of a selection list of possible AE.(31) Thus, standardized AE assessment methods should be established for acupuncture studies.

Risk of bias in included studies

Although, large prospective studies are among the most important sources of safety data, they come with the known risk for information, selection, and confounding bias.(70) Risk of information bias was mostly related to poor reporting of acupuncture regimens and the discrepancies in AE definition and assessment. This is in line with the shortcoming identified for reporting of AE in acupuncture randomized controlled trials.(71) Possible causes of selection bias identified were mainly voluntary participation of practitioners, unsystematic patient selection, and study conductance in highly specialized institutions. Practical reasons make these causes of selection bias inherent to safety studies. They, however, are unlikely to importantly impair external validity, considering the large number of patients and treatments, the variety of countries in which studies were conducted, and the inclusion of different study designs. Future large scale comparative safety studies along with modern statistical methods for confounder adjustment could be used to contrast AE risks related acupuncture to AE risks associated with other treatments and to identify patient and treatment characteristics associated with AE in real world clinical settings.(72)

Limitations

First, it is debatable whether studies should be summarized irrespective of whether AE not necessarily related to acupuncture or adverse reactions likely caused by acupuncture were reported. Another limitation with regard to the inclusion criteria is the restriction to articles published in German or English as many studies on acupuncture are published in Chinese. In order to provide the most comprehensive information possible respective sensitivity analyses were conducted. Additionally, the risk estimates for the different types of minor adverse events are likely to be slightly overestimated and should be interpreted as a rough indication that allows to distinguish frequent from less frequent acupuncture related minor AE. In categorizing the minor AE it was disregarded that several different AE falling in one category could have occurred in the same patient or during the same treatment. Also, calculations of risks in treatments with AE per total number of treatments could not adjust for the fact that multiple AE assessments in the same patient are not independent. Furthermore, zero incidences of certain types of AE were not available. Finally, the causality assessment presented for SAE is limited to expert opinions and is only based on the information provided in the respective article. Such an evaluation does not replace a rigorous causality assessment that would involve querying patients and therapists.

Clinical implications

Patients should be informed that acupuncture commonly causes minor AE, but rarely SAE. Examples for SAE should at least cover the most frequent ones, pneumothorax and strong cardiovascular or vasovagal reactions potentially leading to fall or trauma, along with the respective incidence of 1-3 per million treatments. Patients should also be made aware of the fact that great part of the minor AE are either very mild or even intended effects that indicate a beneficial physiological reactions. However, they should be encouraged to report any prolonged discomfort or pain that are to be avoided during treatment. Acupuncturists should carefully balance treatment intensity according to patients' reactions in order to minimize AE. They should assess local AE upon needle withdrawal and query patients about AE directly after treatment as well as at the subsequent visit. Therapists should be aware that, although uncommon, AE requiring treatment can be expected and necessitate medical decision making. Medical competence is also required for the indication of acupuncture in patients at high risk for AE or those in which AE could lead to particular aversive outcomes such as pregnant women, elderly and patients with cardiovascular comorbidities. In these patients acupuncture can be especially beneficial, as conventional treatments e.g. with analgesics are often limited by side effects or drug interactions, but selection of acupuncture regimens needs to involve careful risk-benefit considerations. Theses medical competences required to provide optimal patient safety should also be reflected by acupuncture education standards and regulations. At this policy makers should take into account the worldwide popularity of acupuncture which is likely to further increase as its scientific level of evidence has led to more than 4000 practice guidelines recommending acupuncture for different mostly pain indications.(69)

Conclusion

Acupuncture can be considered among the safer treatments in medicine. It rarely causes SAE and the majority of the common minor AE are very mild. AE requiring medical management are uncommon. For optimal patient safety acupuncture education standards regulations should reflect that solid medical competence of acupuncturists is required to manage AE properly and to minimize the risk of malpractice. Clinical and methodological heterogeneity calls for an international consensus on AE assessment tools in acupuncture studies and criteria for differentiating acupuncture related AE from therapeutically desired reactions as well as identification of patient related risk factors for acupuncture related AE. In particular, comparative safety studies are needed to contrast acupuncture to standard care in its main indications.

Figure legends

Figure 1: Flow diagram

Designed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)(24)

Figure 2: Risk of bias assessment

Risk of bias assessment was conducted according to Faillie et al.(29) L – green: low risk of bias, U – yellow: unclear risk of bias, H – red: high risk of bias

Figure 3: Meta-analyses of the overall risk for acupuncture related adverse events

Summary risk estimates for adverse events (AE) were calculated as the number of patients or treatments with at least one AE relative to the total number of patients or treatments, respectively. Data on AE reports of patients (pat.) and therapists (ther.) from the article published by Weidenhammer et al. in 2008 were handled separately.

Figure 4: Meta-analyses of the overall risk for serious adverse events related to acupuncture

Summary risk estimates for serious adverse events (SAE) were calculated as the number SAE cases relative to the total number of patients or treatments, respectively. Data from the article published by Weidenhammer et al. in 2008 refer to the AE reports of the therapists (ther.).

Figure 5: Meta-analyses of the overall risk for adverse events (AE) requiring treatment

Summary risk estimates for AE requiring treatment were calculated as the number of patients with such AE relative to the total number of patients.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. DI reports to recieve honorarium and travel costs from non-profit academic organizations, physician chambers and universities for teaching and lecturing and to serve as president of the German Medical Acupuncture Association (Deutsche Ärztegesellschaft für Akupunktur, DÄGfA, a non-profit medical associations). PB declares to recieve honorarium and travel costs from non-profit academic organizations and universities for teaching and lecturing and to be member of the scientific advisory board of the DÄGfA. WZ and TS declare: no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

DI, PB and WZ defined the research question as well as in and exclusion criteria for this systematic review. WZ, TS and PB were responsible for article screening, data extraction and classifications of adverse events. TS and PB performed the quality assessment. Questions and discrepancies were discussed among all authors until consent was achieved. PB conducted the meta-analyses and designed table and figures. All authors contributed to drafting the manuscript and approved its final version for publication.

The corresponding author (PB) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. As the senior author, DI is the guarantor of the work presented in this manuscript. DI accepts full responsibility for the finished article, has access to any data and controlled the decision to publish

Transparency declaration

The lead author DI affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that the review and analyses were conducted as planned.

Ethical approval

As our work represents an analysis of already published data, approval by an ethics committee was not required.

Data sharing

The full set of extracted data and the R-code underlying the meta-analyses are available from the corresponding and senior author (Petra.Baeumler@med.uni-muenchen.de, Dominik.Irnich@med.uni-muenchen.de).

Dissemination to participants and related patient and public communities

Authors plan to disseminate the findings of this review to patients, clinicians, policy makers and the general public through various channels including newsletters, newspapers and magazines. In special regard to patient information, results will be shared during patient seminars and information events, and a concise version of the results will be made available for non-profit acupuncture organisations to be presented on their webpages.

Trial registration

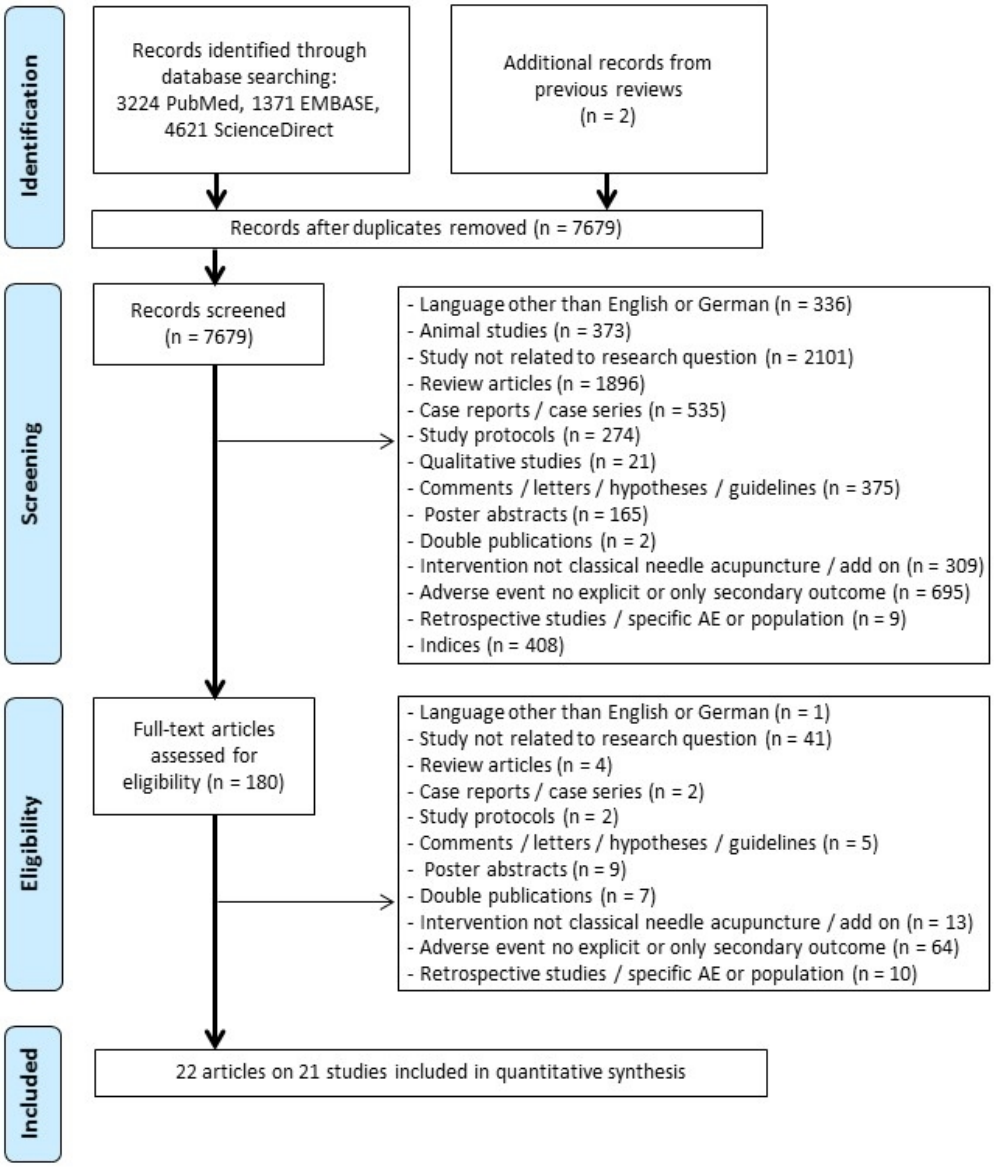
PROSPERO registration number CRD42020151930. To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. It has not been checked for eligibility or for sense by the PROSPERO team.

References

1. Ammon K, Cardini F, Daig U, Dragan S, Frei-Erb M, Hegyi G, et al. Final Report of CAMbrella Work Package 5 - Helath Technology Assessment (HTA) and a map of CAM provision in the EU. CAMbrella - A pan-European research network for Complementary and Alternative Medicine (CAM); 2013 [updated 17.09.2013]. 14]. Available from: https://phaidra.univie.ac.at/view/o:300096.
2. British Acupuncture Council. Acupuncture practitioners in the UK 2016 [updated 2016]. Available from: https://www.acupuncture.org.uk/public-content/about-the-bacc/4115-acupuncture-practitioners-in-the-uk.html.
3. Cui J, Wang S, Ren J, Zhang J, Jing J. Use of acupuncture in the USA: changes over a decade (2002-2012). Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2017;35(3):200-7.
4. Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. J Pain. 2018;19(5):455-74.
5. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev. 2016(6):Cd001218.
6. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Shin BC, et al. Acupuncture for the prevention of tension-type headache. Cochrane Database Syst Rev. 2016;4:Cd007587.
7. Tedesco D, Gori D, Desai KR, Asch S, Carroll IR, Curtin C, et al. Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty: A Systematic Review and Meta-analysis. JAMA surgery. 2017;152(10):e172872.
8. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British journal of anaesthesia. 2008;101(2):151-60.
9. Lee A, Chan SK, Fan LT. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2015(11):Cd003281.
10. Feng S, Han M, Fan Y, Yang G, Liao Z, Liao W, et al. Acupuncture for the treatment of allergic rhinitis: a systematic review and meta-analysis. American journal of rhinology & allergy. 2015;29(1):57-62.
11. Yang A, Wu HM, Tang JL, Xu L, Yang M, Liu GJ. Acupuncture for stroke rehabilitation. Cochrane Database Syst Rev. 2016(8):Cd004131.
12. Smith CA, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. Cochrane Database Syst Rev. 2018;3:Cd004046.
13. Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA. 2018;320(2):167-76.
14. Brinkhaus B, Roll S, Jena S, Icke K, Adam D, Binting S, et al. Acupuncture in Patients with Allergic Asthma: A Randomized Pragmatic Trial. J Altern Complem Med. 2017;23(4):268-77.
15. Whiskey E, Taylor D. A review of the adverse effects and safety of noradrenergic antidepressants. Journal of psychopharmacology (Oxford, England). 2013;27(8):732-9.
16. Carter GT, Duong V, Ho S, Ngo KC, Greer CL, Weeks DL. Side effects of commonly prescribed analgesic medications. Physical medicine and rehabilitation clinics of North America. 2014;25(2):457-70.
17. Chan MWC, Wu XY, Wu JCY, Wong SYS, Chung VCH. Safety of Acupuncture: Overview of Systematic Reviews. Sci Rep. 2017;7(1):3369.
18. White A, Boon H, Alraek T, Lewith G, Liu JP, Norheim AJ, et al. Reducing the risk of complementary and alternative medicine (CAM):Challenges and priorities. Eur J Integr Med. 2014;6(4):404-8.
19. Ren YL, Guo TP, Du HB, Zheng HB, Ma TT, Fang L, et al. A survey of the practice and perspectives of chinese acupuncturists on deqi. Evidence-based complementary and alternative medicine : eCAM. 2015;2015:684708.
20. Shanghai College of Traditional Medicine. Acupuncture - a comprehensive text. Seattle, USA: Eastland Press; 1981.
21. Zhu H. Acupoints Initiate the Healing Process. Medical acupuncture. 2014;26(5):264-70.
22. Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. Am J Med. 2001;110(6):481-5.
23. University of York Y, UK. International prospective register of systematic reviews (PROSPERO). Available from: https://www.crd.york.ac.uk/prospero.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

25. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000;283(15):2008-12.
26. European Medicines Agency. Guideline for good clinical practice E6(R2). 2016. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.
27. the UPPSLA MONITORING CENTRE. WHO-UMC system for standardised case causality assessment. 2013. Available from: https://www.who.int/publications/m/item/WHO-causality-assessment.
28. Council for International organizations of medical sciences - CIOMS. Guidelines for Preparing Core Clinical-Safety Information on Drugs Second Edition – Report of CIOMS Working Groups III and V. 1999. Available from: https://cioms.ch/shop/product/guidelines-preparing-core-clinical-safety-information-drugs-second-edition-report-cioms-working-groups-iii-v/.
29. Faillie JL, Ferrer P, Gouverneur A, Driot D, Berkemeyer S, Vidal X, et al. A new risk of bias checklist applicable to randomized trials, observational studies, and systematic reviews was developed and validated to be used for systematic reviews focusing on drug adverse events. J Clin Epidemiol. 2017;86:168-75.
30. Schwarzer G. meta: {A}n {R} package for meta-analysis. R News. 2007;7(3):40-5.
31. Chung KF, Yeung WF, Yu YM, Kwok CW, Zhang SP, Zhang ZJ. Adverse Events Related to Acupuncture: Development and Testing of a Rating Scale. Clin J Pain. 2015;31(10):922-8.
32. da Silva JBG, Saidah R, Megid CBC, Ramos NA. Adverse events following acupuncture: A prospective survey of 13,884 consultations in a university out-patient acupuncture training clinic in Brazil. Eur J Integr Med. 2014;6(4):488-91.
33. Endres HG, Molsberger A, Lungenhausen M, Trampisch HJ. An internal standard for verifying the accuracy of serious adverse event reporting: the example of an acupuncture study of 190,924 patients. Eur J Med Res. 2004;9(12):545-51.
34. Ernst G, Strzyz H, Hagmeister H. Incidence of adverse effects during acupuncture therapy—a multicentre survey. Complementary therapies in medicine. 2003;11(2):93-7.
35. Furuse N, Shinbara H, Uehara A, Sugawara M, Yamazaki T, Hosaka M, et al. A Multicenter Prospective Survey of Adverse Events Associated with Acupuncture and Moxibustion in Japan. Medical acupuncture. 2017;29(3):155-62.
36. Leung PC, Zhang L, Cheng KF. Acupuncture: Complications are preventable not adverse events. Chin J Integr Med. 2009;15(3):229-32.
37. List T, Helkimo M. Adverse events of acupuncture and occlusal splint therapy in the treatment of craniomandibular disorders. CRANIO. 1992;10(4):318-26.
38. MacPherson H, Scullion A, Thomas KJ, Walters S. Patient reports of adverse events associated with acupuncture treatment: A prospective national survey. Qual Saf Health Care. 2004;13(5):349-55.
39. MacPherson H, Thomas K. Short term reactions to acupuncture--a cross-sectional survey of patient reports. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2005;23(3):112-20.
40. MacPherson H, Thomas K, Walters S, Fitter M. A prospective of adverse events and treatment reactions following 34,000 consultations with professional acupuncturist. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2001;19(2):93-102.
41. Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, et al. Prospective Investigation of Adverse Effects of Acupuncture in 97 733 Patients. Arch Intern Med. 2004;164(1):104-5.
42. Melchart DV, Hager S, Weidenhammer W, Liao JZ, Liu Y, Linde K. Adverse effects and concomitant symptoms associated with acupuncture treatment - A pilot study. Akupunktur. 1998;26(2):87-92.
43. Odsberg A, Schill U, Haker E. Acupuncture treatment: side effects and complications reported by Swedish physiotherapists. Complementary therapies in medicine. 2001;9(1):17-20.
44. Park JE, Lee MS, Choi JY, Kim BY, Choi SM. Adverse events associated with acupuncture: A prospective survey. J Altern Complem Med. 2010;16(9):959-63.
45. Park SU, Ko CN, Bae HS, Jung WS, Moon SK, Cho KH, et al. Short-term reactions to acupuncture treatment and adverse events following acupuncture: A cross-sectional survey of patient reports in Korea. J Altern Complem Med. 2009;15(12):1275-83.
46. Weidenhammer W, Streng A, Melchart D, Linde K. Unerwünschte Wirkungen und Komplikationen bei Akupunkturbehandlung: Ergebnisse der großen Beobachtungsstudie im Rahmen des Modellvorhabens der Ersatzkassen. Dtsch Zeitschrift für Akupunkt. 2008;51(3):6-14.
47. Wen Y, Zhang C, Zhao XF, Deng SZ, He S, Huang LH, et al. Safety of different acupuncture manipulations for posterior circulation ischemia with vertigo. Neural Regen Res. 2016;11(8):1267-73.

48. White A, Hayhoe S, Hart A, Ernst E. Survey of adverse events following acupuncture (SAFA): A prospective study of 32,000 consultations. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2001;19(2):84-92.
49. Witt CM, Pach D, Brinkhaus B, Wruck K, Tag B, Mank S, et al. Safety of acupuncture: Results of a prospective observational study with 229,230 patients and introduction of a medical information and consent form. Forsch Komplementmed. 2009;16(2):91-7.
50. Yamashita H, Tsukayama H, Hori N, Kimura T, Tanno Y. Incidence of adverse reactions associated with acupuncture. J Altern Complem Med. 2000;6(4):345-50.
51. Yamashita H, Tsukayama H, Tanno Y, Nishijo K. Adverse events in acupuncture and moxibustion treatment: A six-year survey at a national Clinic in Japan. J Altern Complem Med. 1999;5(3):229-36.
52. Zhao L, Zhang FW, Li Y, Wu X, Zheng H, Cheng LH, et al. Adverse events associated with acupuncture: Three multicentre randomized controlled trials of 1968 cases in China. Trials. 2011;12:no pagination.
53. Degner D, Grohmann R, Kropp S, Ruther E, Bender S, Engel RR, et al. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry. 2004;37 Suppl 1:S39-45.
54. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. American journal of therapeutics. 2000;7(2):115-21.
55. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. Bmj. 2011;342:c7086.
56. Martin Arias LH, Martin Gonzalez A, Sanz Fadrique R, Salgueiro Vazquez E. Gastrointestinal safety of coxibs: systematic review and meta-analysis of observational studies on selective inhibitors of cyclo-oxygenase 2. Fundamental & clinical pharmacology. 2018.
57. Wang C, Tan B, Williams A. Safety and side effects of acupuncture therapy in Australia: A systematic review. Eur J Integr Med. 2019.
58. Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. Pediatrics. 2011;128(6):e1575-87.
59. Wang CC, Tan JY, Williams A. Safety and side effects of acupuncture therapy in Australia: A systematic review. Eur J Integr Med. 2019;27:81-9.
60. Tan JY, Molassiotis A, Wang T, Suen LK. Adverse events of auricular therapy: a systematic review. Evid Based Complement Alternat Med. 2014;2014:506758.
61. Zhang J, Shang H, Gao X, Ernst E. Acupuncture-related adverse events: a systematic review of the Chinese literature. Bull World Health Organ. 2010;88(12):915-21C.
62. Xu S, Wang L, Cooper E, Zhang M, Manheimer E, Berman B, et al. Adverse events of acupuncture: a systematic review of case reports. Evid Based Complement Alternat Med. 2013;2013:581203.
63. He W, Zhao X, Li Y, Xi Q, Guo Y. Adverse events following acupuncture: a systematic review of the Chinese literature for the years 1956-2010. J Altern Complem Med. 2012;18(10):892-901.
64. Ernst E, Lee MS, Choi TY. Acupuncture: does it alleviate pain and are there serious risks? A review of reviews. Pain. 2011;152(4):755-64.
65. Ullah W, Ahmad A, Mukhtar M, Virk HUH, Sarwar U, Figueredo V. Acupuncture-Related Cardiac Complications: A Systematic Review. J Invasive Cardiol. 2019;31(4):E69-E72.
66. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ. 2006;333(7568):597-600.
67. Zhu HZ. Running a Safe and Successful Acupuncture Clinic. Edinburgh, London, New York, Oxford, Philadelphia, St Louis, Sydney, Toronto: Elsevier - Churchill Livingstone; 2006.
68. Deng L, Gan Y, He S, Ji X, Y. L, Wang R, et al. Chinese Acupuncture and Moxibustion. 2nd ed. Beijing, China: Foreign Languages Press; 1999.
69. Schwaneberg T, Witt CM, Roll S, Pach D. Comparing physicians' and patients' reporting on adverse reactions in randomized trials on acupuncture-a secondary data analysis. BMC Complement Altern Med. 2019;19(1):223.
70. Suissa S. Statistical methods in pharmacoepidemiology: advances and challenges. Stat Methods Med Res. 2009;18(1):3-6.
71. Capili B, Anastasi JK, Geiger JN. Adverse event reporting in acupuncture clinical trials focusing on pain. Clin J Pain. 2010;26(1):43-8.
72. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. Bmj. 2019;367:l5657.



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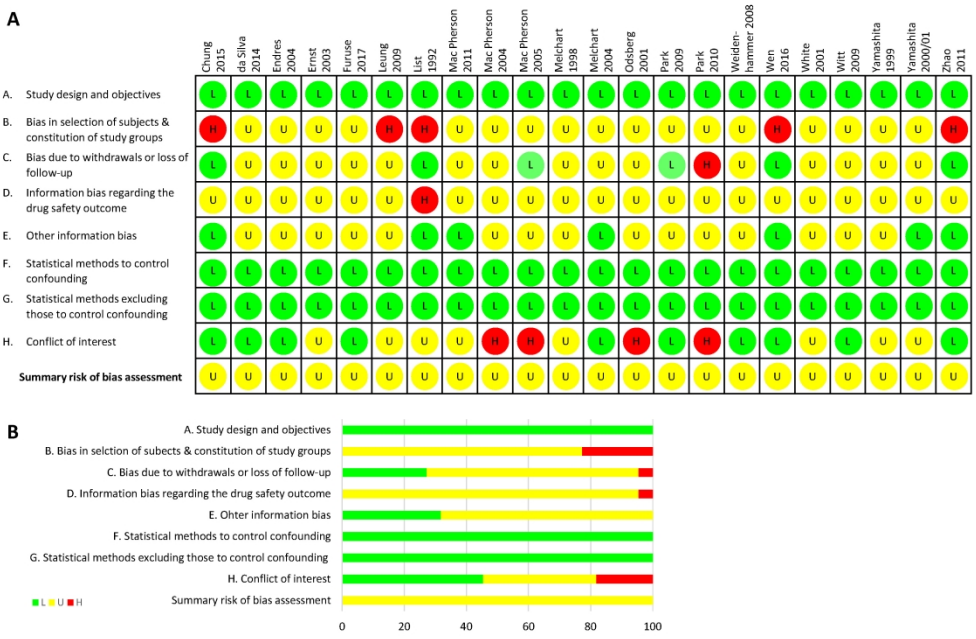

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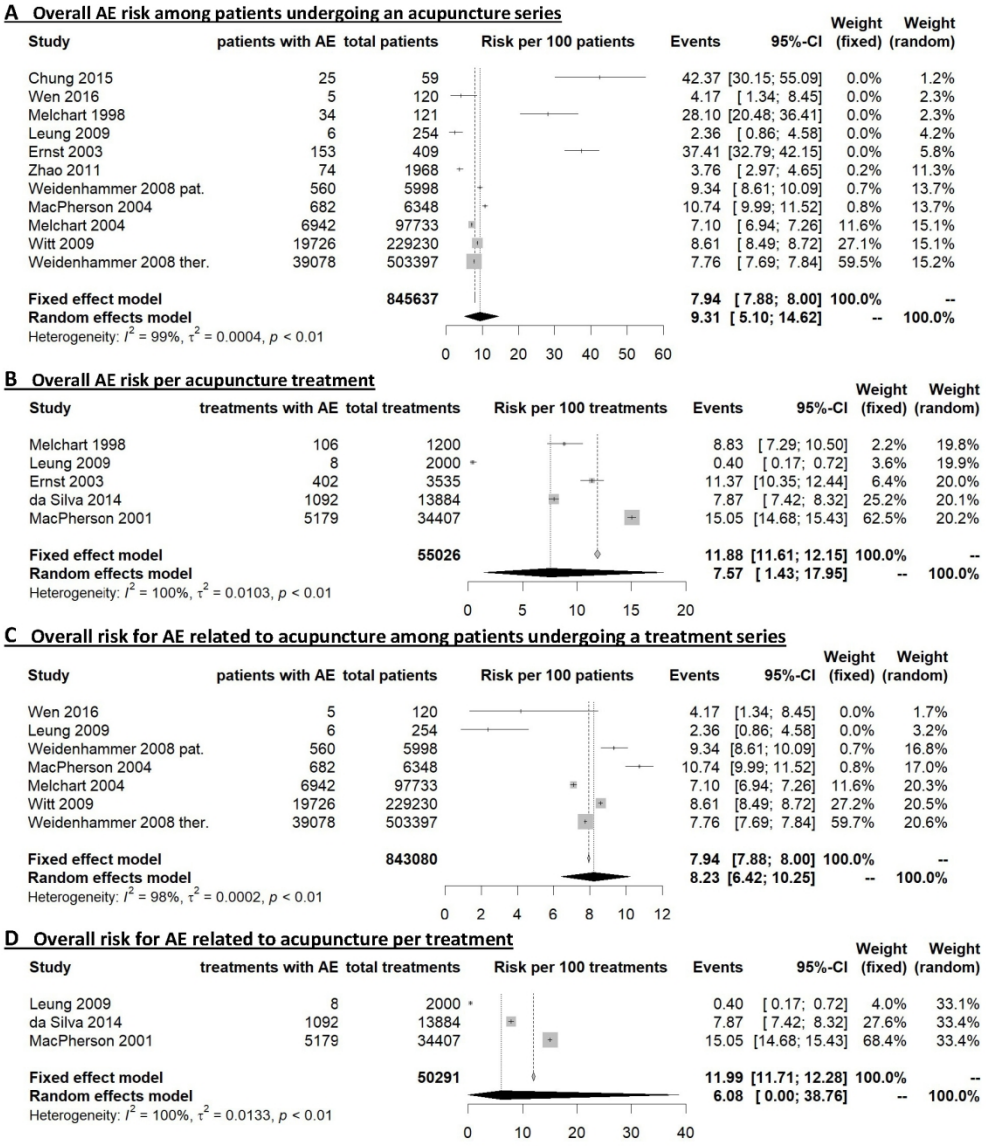

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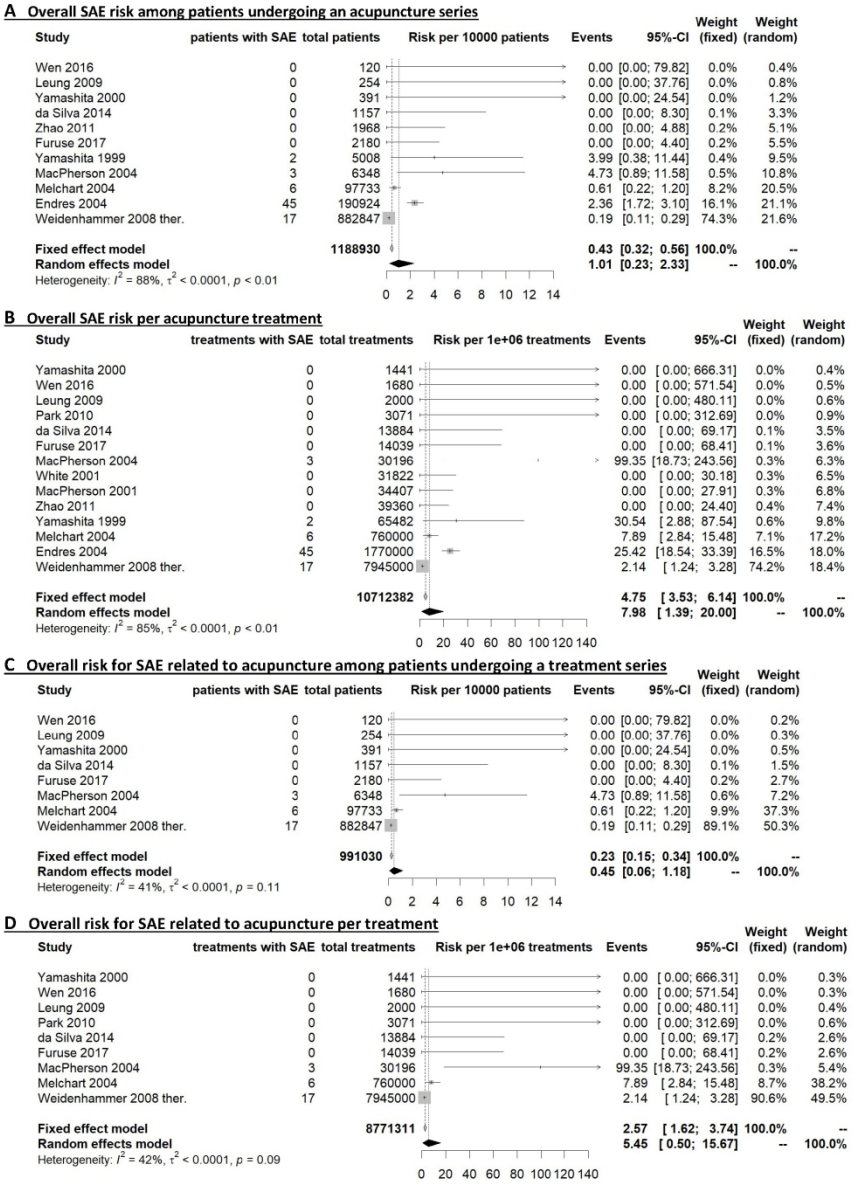

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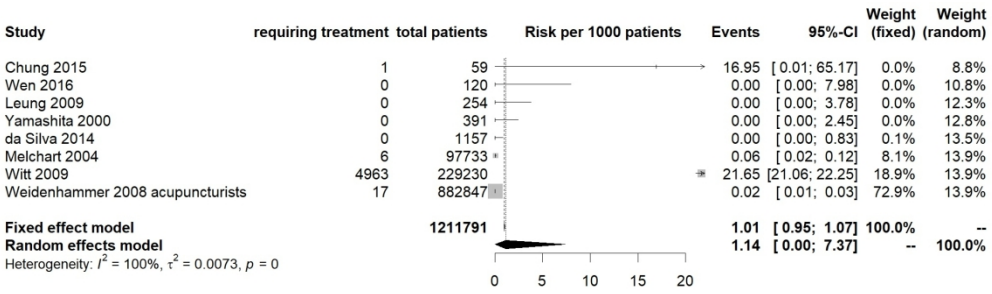


286x82mm (180 x 180 DPI)

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

University of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Acupuncture related adverse events - a systematic review of prospective clinical trials

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

English

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.
19/09/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.
31/12/2019

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Piloting of the study selection process

Piloting of the study selection process

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Dr. Petra Bäumler

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Petra

7. * Named contact email.

Give the electronic email address of the named contact.

Petra.Baeumler@med.uni-muenchen.de

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Dr. Petra Bäumler

Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich

Pettenkoferstr. 8a

80336 Munich, Germany

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

0049-89-4400-53625

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Petra Baeumler. Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich
Professor Dominik Irnich. Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich
Mrs Theresa Stübinger. Multidisciplinary Pain Center, Department of Anaesthesiology, Universtiy Hospital LMU Munich

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

No funding is received

State the funder, grant or award number and the date of award
Grant number(s)

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

Yes

Petra Bäumler and Dominik Irnich receive honoraria and travel costs from non-profit academic organizations, physician chamber and universities for teaching and lecturing. Theresa Stübinger declares no conflict of interest

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Wenyue Zhang. School of Acupuncture, Moxibustion and Tuina, Beijing University of Chinese Medicine

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the risk for minor and serious adverse events caused by acupuncture?

What kind of adverse events can be caused by acupuncture?

What is the risk of the different types of acupuncture related adverse events?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Databases: PubMed, Scopus, EMBASE

Publication period: inception to 15th September 2019

Search Terms: acupuncture, adverse event(s), adverse effect(s)

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Acupuncture is the insertion of fine needles at certain points, so called acupuncture points, on the patients body for therapeutic or preventive purposes. Acupuncture originates from ancient Chinese medicine, but is nowadays used worldwide in many different variations. There is level 1 for its effectiveness in acute and chronic pain. Needles are stimulated manually, electrically. Often moxibustion is used as an adjunct. The safety of acupuncture has been debated, and surely needle penetration can cause harms, such as tissue damage, peripheral nerve injury and bleeding. In comparsion to analgesic drugs for example, risk and consequences of adverse events are deemed minor, but reviews on the safety of acupuncture are either outdated or lack an assessment of study quality.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Humans treated by needle acupuncture

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Acupuncture involving either manual or electrical needle stimulation with or without moxibustion

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

As the aim of this review is to estimate the crude risk of acupuncture related adverse events, comparator group data are not relevant.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Inclusion criteria:

Prospective study

Primary outcome is the risk of acupuncture related adverse events

Treatment involves acupuncture with needles that are stimulated manually or electrically either in combination with or without moxibustion

Articles published in English or German before 15th of September 2019

Exclusion criteria

Treatment involves injection

Treatment involves skin penetration with any other device than classcial acupuncture needles such as press needles, cauterization devices etc.

Treatment is restricted to non-penetrating stimulation such as laser acupuncture, acupressure, transcutaneous electrical nerve stimulation or moxibustion

Treatment is restricted to particular body parts associated with low risk of adverse events such as auricular or one-point acupuncture

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Risk of serious and minor acupuncture related adverse events (AE) as number of AE per treatment and patients with AE per 100.000 patients treated

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

adverse events ocurring during or after acupuncture treatment

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Type of adverse events caused by acupuncture

Risk of the different types of acupuncture related adverse-events

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

adverse Events ocurring during or after acupuncture treatment

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Incidence of acupuncture related adverse events will be extracted as the number of adverse events per treatment and as number of patients experiencing these adverse events per the total number of patients treated. Data extraction will be performed by two independent reviewers who will extract all available data on acupuncture related adverse events from identified studies. This includes extraction of the total number of and/or patients with minor and serious adverse events as well as extraction of the numbers of and/ or patients with all types of adverse events separately in relation to the number of treatments and/or total number of patients treated. The different types of adverse events will be categorized into supersets of adverse events whose risk is calculated separately.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Included studies will be assessed for risk of bias according to a checklist developed by Faillie and colleagues for systematic reviews focusing on adverse events.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will provide the reader with the range (min and max) and the median of the total risk to suffer from an minor and serious adverse event during or after acupuncture treatment that was identified by the studies. The same measures will be provided for the risks of the supersets of adverse events identified from the different studies.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

It is likely that certain subsets of patients are at a higher risk for acupuncture related adverse events. According to the obtained results we will provide characteristics and separate summaries of studies including patients with a high and low risk profile.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews

No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
Yes

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.
Germany

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

The review has not been registered elsewhere.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

A paper presenting the review results will be submitted to a journal listed in MEDLINE. Furtermore, results will be published at international congresses.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

acupuncture, adverse-event, adverse-effect, safety, needling, moxibustion, traditional Chinese mecicine

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint. List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2 / 4 / 19
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 / 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 / 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 - 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 Figure 2A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3 - 5 Table 2 / 4 Suppl. S6 / S7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9 - 12 Figure 3 - 5 Table 4 Suppl. S6 / S7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 Figure 5 B
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 - 12 Figures 3C/D 4C/D
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	page5 table 1
4	Type of exposure or intervention used	page5 table 1
5	Type of study designs used	page5 table 1
6	Study population	page5 table 1
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	title page
8	Search strategy, including time period included in the synthesis and key words	page 5
9	Effort to include all available studies, including contact with authors	page 5
10	Databases and registries searched	page 5
11	Search software used, name and version, including special features used (eg, explosion)	none
12	Use of hand searching (eg, reference lists of obtained articles)	page 5
13	List of citations located and those excluded, including justification	table1 figure 1
14	Method of addressing articles published in languages other than English	page 5
15	Method of handling abstracts and unpublished studies	figure 1
16	Description of any contact with authors	none
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	pages 4, 5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	page 5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	page 5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	n.a.
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	page 6
22	Assessment of heterogeneity	page 6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	page 6
24	Provision of appropriate tables and graphics	Tables 1-4, figures 1-5 Suppl. S1-7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	figs 3-5
26	Table giving descriptive information for each study included	page 7 table 1
27	Results of sensitivity testing (eg, subgroup analysis)	pages 10-12 figures 3-5
28	Indication of statistical uncertainty of findings	pages 10-12 figures 3-4

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	pages 14-15 Suppl. S4
30	Justification for exclusion (eg, exclusion of non-English language citations)	page 16
31	Assessment of quality of included studies	page 15
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Pages 14-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	page 16
34	Guidelines for future research	pages 15 - 16
35	Disclosure of funding source	page 18

Bleeding		
• Bleeding • Bleeding at needling site • Mild / transient / minor bleeding • Subcutaneous bleeding • Hematoma • Minor hematoma • Subcutaneous / superficial hematoma	• Small hemorrhage • Lesion of blood vessel • Bruising • Bruising at needling site • Mild / transient bruising • Heavy bruising • Subcutaneous bruise	• Ecchymosis or hematoma accompanied by pain • Ecchymosis or hematoma without pain • Petechia or ecchymosis
Local pain		
• Pain • Needle (-site) pain • Pain where needle was inserted / at the site of the needle / in the punctured region • Mild / transient pain at needling site • Severe / strong / significant pain at needling site	• Pain upon insertion / stimulation • Pain while needle was in place • Pain upon needle withdrawal at the acupuncture point • Pain after needle was removed • Remaining / residual needle site pain • Prolonged / unacceptable pain at needle site	• Mild pain at the acupuncture site more than one hour after treatment • Pain disappearing after > 3 days • Chest pain (pneumothorax ruled out) • Electroacupuncture problems e.g. too strong current resulting in pain • Local muscle pain • Unknown pain
Other local AE		
• Wheal • (Local) swelling • Redness • Flare • Localized erythema • Needle-site / local skin reaction • (Skin) irritation at acupuncture point • Skin infection • Local (skin) infection	• Inflammation at application site • Itch • Itching and redness • Itching in the punctured region • Itching and erythema (suspected contact dermatitis) • Local allergic reaction (uticaria) • Needle allergy • Allergic phenomena / reaction	• Significant rash on abdomen few days after acupuncture • Cellulitis after treatment of edematous leg • Edema in m. tibialis with anterior toe lifting weakness (fully resolved) • Other local AE (around the acupuncture site)
Central nervous system		
• Aphasia • Dizziness • Mild / transient dizziness • Imbalance • Severe dizziness, vertigo or loss of balance	• Vertigo • Disorientation (length unspecified, 1 h, 1 day) • Severe disorientation • Disturbed speech • Slurred speech	• Disturbed vision • Spontaneous sensory perceptions • Shivering • Seizure shortly after treatment • Tremor
Peripheral nervous system		
• Cold sensation at needling site • Feeling of acupuncture point at contralateral arm • Paraesthesia • Temporary paraesthesia • Tingling • Tingling, prickling, burning, dysesthesia	• Prolonged deqi • Strong acupuncture or heavy sensation • Hypaesthesia • Numbness • Numbness in upper extremity • Numbness and unusual sensation • Severe stiffness or numbness	• Hypaesthesia with numbness for three days • Insensibility • Itching, pins & needles, tingling or burning sensation • Nerve irritation • Neuritis
Aggravation of symptoms		
• Aggravation • Aggravation of complaints / existing ailment / existing symptoms • Unexpected, severe or prolonged worsening of symptoms • Aggravation of symptoms during acupuncture session / after treatment	• Transient aggravation of symptoms • Aggravation of existing symptoms followed by improvement • Deterioration / exacerbation of symptoms • General aggravation of symptoms • Worsening of health state	• Worsening of condition (after removing needles) • Headache and or facial pain • pressure and or tension in the teeth • Increased pain
Vegetative nervous system		
• (Generalized) sweating • Isolated sweating of hands • Mild sweating • Flushed cheeks and body warmth • Hot flash • Feeling of warm / heat / cold • Coldness / feeling cold • Freezing • (Feeling of) fatigue • Extreme feeling of fatigue • Feeling tired (mild transient) • Tiredness and exhaustion	• Abnormal tiredness • Severe / significant tiredness or exhaustion • Lethargy • Dazed • Vasovagal reaction: collapse, dizziness, nausea & vomiting • Unconsciousness • Fainting • Faint / dizzy • Feel faint / drowsy • Feel faint (significant)	• Significant / severe drowsiness • Drowsiness not causing hazard • Prolonged drowsiness (one day, one week) • Drowsiness or restlessness • Orthostatic problems • Malaise • Poor concentration • Dry lips / mouth • Xerostomia • Hunger / thirst

Motor system		
• Cramp	• Heavy legs	• Joint problems
• General muscle tenderness	• Knee went weak	• Restricted movement
• Muscle spasm / tension / weakness	• Weakness in legs / legs or arms	• Stiffness
Distant pain		
• Pain / ache / discomfort other than at needling site	• Mild transient pain not at needling site	• Generalized muscle pain
• Reactive pain at other body sites	• Chest pain / tightness	• Other / unspecified pain / aches
Gastrointestinal / gynaecological system		
• Nausea	• Tiredness next day after ten hours of diarrhoea (significant)	• Increased peristalsis
• Mild and transient nausea	• Stomach ache	• Loss of appetite
• Severe nausea	• Abdominal distension	• Other gastrointestinal complaints
• Vomiting	• Impaired bowel function	• Increased haemorrhage during menses
• Severe vomiting	• Digestive problems	• Menstrual problems
• Constipation	• Entero- / gastrospasm	
• Diarrhoea		
Cardiovascular system		
• Cardiovascular / circulatory problems	• Increase in blood pressure	• Tachycardia
• Depression of blood pressure	• Palpitation	• Other cardiac disturbances
Respiratory system		
• Asthma attack	• Breathing difficulties	• Bronchitis or airway problems
Generalized skin reactions		
• Dermatological problems	• Other dermatological phenomena	
Headache		
• Headache	• Headache for three days	• Severe headache or migraine
• Headache the next day	• Migraine attack	
Emotional interference		
• Aggressive behaviour	• Depressive mood	• Severe emotional outburst and anger at practitioner
• Anxiety	• Discomfort	• Fear
• Anxiety and panic (up to one hour)	• Restlessness or nervousness	• Grief / crying / tearful
• Significant panic with sensation of heat and sweatiness	• Disorientation, anxiety, nervousness, insomnia or emotional	• Needle phobia, anxiety and rage
• Severe panic / agitation / depression with anxiety	• Emotional /psychological reaction	• (Severe) nightmares
• Depressed emotional state or neurovegetative dystonia	• (Uncontrolled) euphoria	• Other mood swings
	• Significant emotional release (manic, relaxed, rage or confusion)	
Sleeping problems		
• Sleep disturbances	• Severe sleeping problems	• Insomnia
• Impaired sleep	• Severe sleeplessness	
Moxa caused adverse events		
• Burn injury	• Burns	• Blister following moxibustion
Needling malpractice		
• Left alone / unattended in the treatment room for too long	• Failure to remove needle(s)	
• Broken needle	• Forgotten / dropped needle	
• Stuck or bent needle	• Needle lost or forgotten	
Other or unclassified adverse events		
• Change of symptoms	• Nose bleeding	• Additional comments
• Illness	• Miscellaneous symptoms	• Other systematic symptoms
• Sick	• Haematuria on next day	• Other neurological problems
• (Systemic) infection	• Increased urinary frequency	• Others / unspecified / other (mild) adverse events
• Fever	• Concomitant diseases of recent appearance	• other negative reactions
• Angina	• Change of taste	• Unknown due to incomplete record form
• Eye irritation	• Change of weight / weight reduction	
• Irritated tongue		

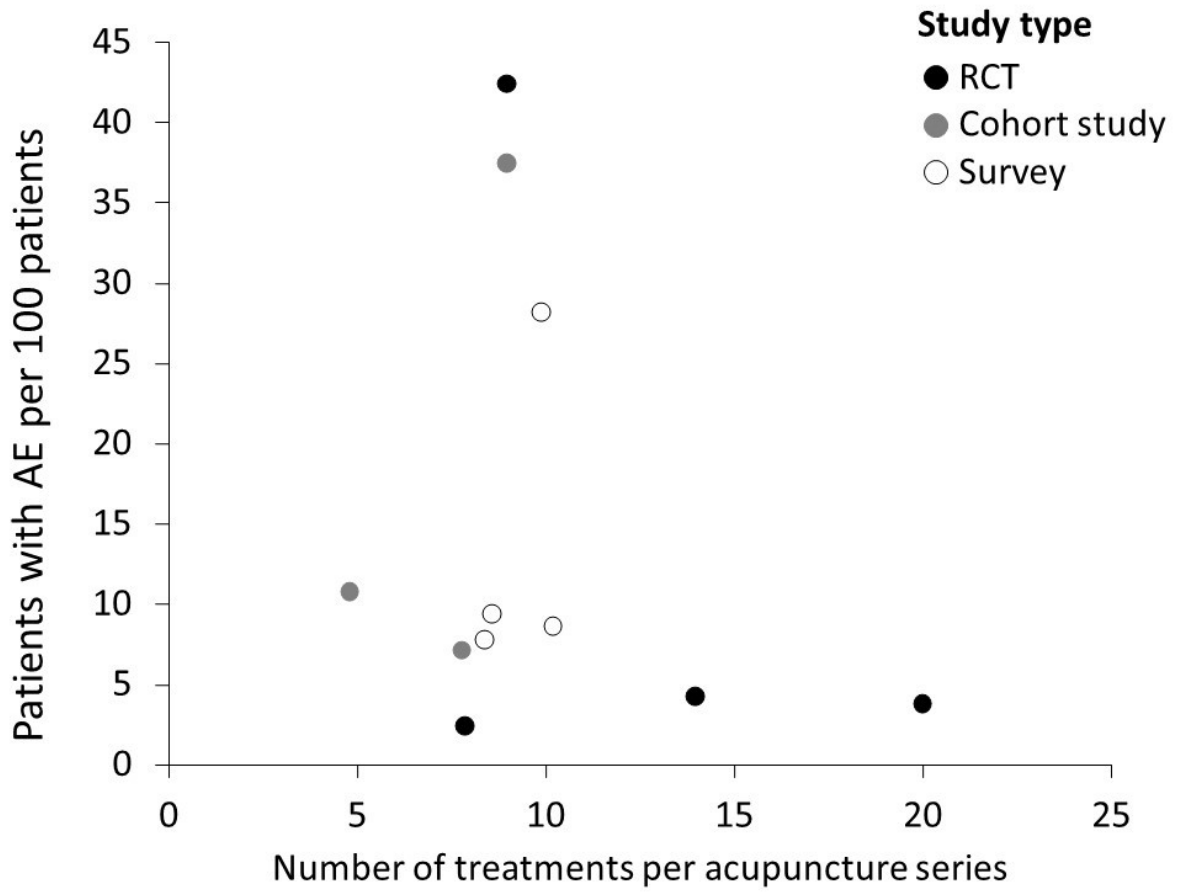
Online supplementary appendix S3: Categorization of adverse events

Subheadings represent the categories to which adverse events (AE) were assigned. AE descriptors extracted from the included publication are reported verbatim or in spirit in order to provide an overview of the different wordings concerning AE type and severity. Slashes indicate that expressions were also used separately. Terms in brackets indicate that such terms were not used in all of the descriptors with otherwise similar wording.

Study	AE definition (*direct quotes* with eventual comments)	Severity rating (*direct quotes* with eventual comments)
Chung 2015	*"Participants were asked the acupuncture AEs by acupuncturists using an open-ended question first, then the AcupAE. The open ended question asked if they had any discomfort during treatment and after the last few treatments."*	*"…mild AE required no treatment or resolved within 1 day, moderate AE lasted more than 1 day or relieved by non-prescription medication, severe AE required medical treatment."*
Da Silva 2014	*"Adverse effects were defined as 'any unusual, inconvenient or ill-effect, no matter how small, that is unintended and non-therapeutic', Examples were given to patients"; "We did not included 'aggravation of symptoms' because of the difficulty in judging whether the event was associated with acupuncture, was serious or not, and also because some practitioners believe that transient worsening is part of treatment."*	*"A 'serious event' was considered as one which needed further specific medical intervention or had interfered with the patient's normal life for at least the remainder of the day"*
Endres 2004	*"The ICH definition of an adverse event (AEs) is any untoward medical occurrence experienced by patients, temporally but not necessarily causally associated with the use of a drug or medical treatment…"*	*"… serious adverse event (SAEs) identified, according to the ICH, as an adverse event that results in a life-threatening condition or death, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity, including congenital anomaly/birth defects"*
Ernst 2003	*"A checklist was provided which mentioned haemorrhage, haematoma, infections, neurological abnormalities, fainting, vestibular symptoms, nausea, prolonged DeQi effect and increase of pain. Free space was provided to record other observed adverse effects. All therapists asked their patients with standardised open questions: during therapy, "How do you feel now?"; and before every subsequent therapy, "How did you feel after the last acupuncture therapy?". The therapists were asked to document 'possible septic syndrome' if fever and/or hypotension were observed in combination with local infection at one or more points that had been needled."*	SAE not defined
Furose 2017	*''…any untoward medical occurrence in a patient who underwent acupuncture therapy and which does not necessarily have a causal relationship with this treatment.''* In line with ICH but only selection list with AE likely related to acupuncture applied	*"…serious AE (pneumothorax, other organ injury, central nerve injury, peripheral nerve injury, suppurative arthritis, suppurative myositis, cellulitis, hepatitis B, hepatitis C, needle breakage and/or needle migration, accidental insertion, and other symptoms that practitioners regarded as serious)…"*
Leung 2009	*"A list of possible complications and adverse effects was used to check the events thoroughly. The list consisted of bleeding, obvious tissue/ organ damage, fainting, syncope, persistent needle pain, post-puncture tiredness, palpitation, exacerbation of symptoms nausea, dyspnea, convulsion, psychological symptoms, etc."*	SAE not defined *"no harmful complication was encountered"*
List 1992	*"In this paper, adverse event refers to any reaction to a treatment besides the intended treatment effect irrespective of any correlation between the treatment and the reaction."*	SAE not defined
Mac Pherson 2001	*"Practitioners were asked to record mild transient reactions to treatment, within one or more of three categories (systemic, aggravation, local)"*	*"…'significant adverse event' was defined as any event that was 'unusual, novel, dangerous, significantly inconvenient, or requiring further information'…"*
Mac Pherson 2004	*"For the purposes of this survey we did not define an adverse event but, instead, provided patients with a checklist of possible events. This and the overall questionnaire, while not formally validated, were developed from two practitioner surveys."*	*"In contrast, ''serious adverse events'' were predefined as those resulting in admission to hospital or being permanently disabling or life threatening"*
Mac Pherson 2005	*"Patients were asked to report short term reactions, by answering the question: 'Thinking about the visit at which you were given this form, did you experience during or immediately after your acupuncture any of the following?' We provided a checklist of possible short term reactions drawn from the results of two recently published practitioner surveys."*	SAE not defined
Melchart 1998	*„Der Fragebogen sollte, der Erfahrung der behandelnden Ärzte entsprechend vergleichsweise häufige Ereignisse erfassen, die aus Patientensicht im allgemeinen als unangenehm oder unerwünscht beurteilt werden"* English translation: The questionnaire was designed to reflect relatively frequent events that are, according to the physicians' experience, often experienced as unpleasant or adverse by the patient.	SAE not defined
Melchart 2004	*"…physicians had to report whether an adverse effect (defined as any adverse event possibly related to acupuncture) occurred. If this was the case, the adverse effect had to be specified. Predefined categories were bleeding, needling pain, hematoma, infection orthostatic problems, forgotten needles, and any other events."*	*"Serious adverse effects (defined as any adverse effects possibly related to acupuncture making treatment necessary or severely interfering with the patient's wellbeing, eg a pneumothorax or a nerve injury)…"*
Odsberg 2001	*"Negative side effect – a non-intended effect of the acupuncture treatment that the patient experiences as negative, i.e. haematoma and fainting."*	*"Complication – a non-intended effect of the acupuncture treatment that may threaten the patient's life, i.e. pneumothorax."*
Park 2009	*"Therefore, this study has surveyed to report on short-term reactions as well as de qi, side-effects, and the satisfaction of patients following acupuncture treatment.", "After explaining the purpose of the survey to the patients, we had them fill out a survey form querying their reactions…"*	*SAE not defined*

Park 2010	*"According to the World Health Organization (WHO), an AE is described as ''any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.'',* *"In the AE section, the reporter was asked to describe when the AEs appeared and disappeared, the type and details of the AE, and the treatment for the AE. Two (2) types of AE were identified: local AEs and systemic AEs….", "Local AEs included a broken or forgotten needle, hemorrhage, needle allergy, needle-site pain, hematoma, and a stuck or bent needle. Systemic AEs included drowsiness, fainting, fever, hypotension, nausea, vomiting, diarrhea, sweating, headache, discomfort, dizziness, anxiety and panic, seizure, insensibility, mental disturbance, pain, temporary paresthesia, pneumothorax, organ or tissue injury, hepatitis B/C, otitis externa, sepsis, central nerve injury, skin infection, or symptom aggravation."*	*"The International Conference on Harmonization guidelines define a serious AE as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is a congenital anomaly/birth defect.18 There were no serious AEs related to acupuncture in this study."*
Weiden-hammer 2008	*„Außerdem wurde gefragt: „Welche unerwünschten Wirkungen oder Komplikationen der Akupunktur sind aufgetreten?" Antwortoptionen waren hier: „Blutung", „Nadelschmerz", „Hämatom", „Infektionen", „Kreislaufprobleme", „vergessene Nadeln" und „andere" (mit Freitextfeld zur Beschreibung des Ereignisses)."* English translation: Furthermore it was asked „Which adverse effects or complications occurred through acupuncture?" Response options were: 'bleeding', 'needling pain', 'haematoma', 'infections', 'circulatory problems', 'forgotten needles' and 'others' (with free text for a description of the event)	*"Als schwerwiegende unerwünschte Therapiewirkungen waren alle Ereignisse zu bewerten, die a) möglicherweise in einem kausalen Zusammenhang mit der Akupunkturbehandlung standen und b) behandlungspflichtig waren oder/und den Patienten gravierend beeinträchtigten oder gefährdeten (z. B. Pneumothorax, Nervenläsion)."* English translation: Serious adverse treatment effects were defined as events that a) had a possibly causal relationship with the acupuncture treatment and b) required treatment and/or compromised or threatened the patient seriously (e.g. pneumothorax, nerve lesion).
Wen 2017	*"Adverse events, including pain, hematoma, perforation, bleeding, fainting, local infection, abscess, or breakage or retention of the needle after treatment, were recorded after every session."*	SAE not defined
White 2001	*"We defined an adverse event as 'any ill-effect, no matter how small, that is unintended and nontherapeutic'. This definition was used both in order to identify events that occurred through error but were not reactions to acupuncture, and in order to include minor events such as bleeding, not just serious events, even when these may have been an expected consequence of needling. We decided not to record unintended beneficial or pleasant events.", "…number of adverse events classified under specific headings…", "Some practitioners regard aggravation or drowsiness as a part of the response to treatment (the 'healing crisis'), and not as unintended 'adverse' events. Therefore, if a patient later improved substantially, respondents were instructed to convert the relevant mark in the box to an asterisk."*	*"Significant Event Report….to record any event that was 'unusual, novel, dangerous, significantly inconvenient or requiring further information'. Examples were provided, which included needling problems (broken or forgotten needle, moxa burns), systemic effects (faint, convulsion, drowsiness causing hazard e.g. on the road, severe nausea) and symptoms (unexpected or prolonged aggravation)."*
Witt 2009	*"At the end of each treatment cycle, all patients were asked to complete a standardised questionnaire and to document adverse events they associated with acupuncture (defined as adverse effects) in free text and, if necessary, the kind of treatment they had needed (self-treatment, medication/physician treatment, treatment in hospital). Adverse events without association to the acupuncture treatment were not documented."*	*"Patients who reported adverse effects which needed treatment, received from the study office an additional, more detailed standardised questionnaire concerning their most important adverse effect."*
Yamashita 1999	*"We defined AE as an unfavorable medical event that occurred during or after the treatment regardless of causal relationships [Beam 1992]"*	*"…no serious or severe cases of negligence such as pneumothorax or spinal cord injury were reported in the TCT Clinic But 2 cases identified from reports that required hospitalization / likely to have caused disability."*
Yamashita 2000	*"The acupuncturists meticulously observed the punctured region and general condition of the patients during and immediately after treatment. The patients were asked to report any pain or discomfort caused by needle insertion. In the interview after each treatment session, the acupuncturists asked the patients, "Did you feel any discomfort during today's treatment session, or do you have now such a feeling that did not exist before the treatment session? Please tell me every slight discomfort even if you don't think it is a problem." A similar question was asked at the patient's next visit, "Did you feel any discomfort that may have had something to do with the previous treatment, after you left our clinic?"*	*"Details recorded on the report form included … severity or magnitude of symptom, and treatment for the reaction.",* *"All reactions were mild and transient."* *"No medical care was required for any of these reactions."*
Zhao 2011	*"AE is defined as an unfavourable medical event that occurs during or after the treatment regardless of causal relationship",* *"AE and SAE were defined a priori from the literature and the State Food and Drug Administration (SFDA) in China."*	*"Serious adverse effects (SAEs) refers to those that caused hospitalisation, extended duration of hospitalisation, disability, impaired ability to work, death or were life threatening, resulting in events such as congenital malformations in the process of the clinical trials."*

Online supplementary appendix S4: Definition of adverse events with respective severity ratings as direct quotes from the included manuscripts



Online supplementary appendix S5: Independence of incidences of adverse events per patient from the number of treatments per acupuncture series and study type

Scatterplot of the number of treatments applied within an acupuncture series against the observed adverse events (AE) incidence as patients with AE per 100 patients

Study	Total number of patients	Risk as patients with AE per 100 patients [95%-CI]									
		Bleeding	Needle sit pain	Other local AE	Vegetative reaction	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal / gynaecologcial system	Unclassified AE
List 1992	29		44.83 [27.46; 62.87]		58.62 [40.52; 75.59]	93.10 [81.26; 99.30]	37.93 [21.45; 55.99]	27.59 [13.14; 44.96]		17.24 [5.94; 32.83]	3.45 [0.00; 12.99]
Chung 2015	59	15.25 [7.30; 25.45]	32.20 [20.99; 44.57]	35.59 [23.97; 48.14]	13.56 [6.10; 23.38]		5.08 [0.99; 12.08]	11.86 [4.94; 21.26]		5.08 [0.99; 12.08]	3.39 [0.33; 9.47]
Wen 2016	120	0.83 [0.00; 3.24]	2.50 [0.48; 6.04]						0.83 [0.00; 3.24]		
Melchart 1998	121	3.31 [0.88; 7.21]	14.05 [8.46; 20.78]	1.65 [0.16; 4.68]	8.26 [4.05; 13.81]	10.74 [5.88; 16.85]	2.48 [0.48; 5.99]	0.83 [0.00; 3.21]	0.83 [0.00; 3.21]	4.13 [1.33; 8.39]	
Leung 2009	254	2.36 [0.86; 4.58]									
Yamashita 2000	391		0.26 [0.00; 1.00]	1.02 [0.27; 2.26]	11.76 [8.76; 15.14]	2.81 [1.41; 4.68]	0.77 [0.15; 1.87]				
Ernst 2003	409	25.18 [21.10; 29.50]	8.07 [5.63; 10.90]	0.24 [0.00; 0.96]	6.36 [4.20; 8.92]	0.98 [0.26; 2.16]	6.11 [4.00; 8.64]	4.89 [3.01; 7.19]		1.96 [0.84; 3.52]	17.85 [14.29; 21.70]
Zhao 2011	1968	3.40 [2.65; 4.25]	0.05 [0.00; 0.20]		0.10 [0.01; 0.29]		0.05 [0.00; 0.20]			0.05 [0.00; 0.20]	
Furuse 2017	2180	12.80 [11.43; 14.23]	6.24 [5.26; 7.29]			1.06 [0.67; 1.53]					1.10 [0.71; 1.58]
Weidenhammer 2008 patients	5998	0.48 [0.32; 0.67]	0.32 [0.19; 0.47]	0.32 [0.19; 0.47]	2.72 [2.32; 3.14]	0.80 [0.59; 1.04]	0.90 [0.68; 1.16]	0.47 [0.31; 0.66]	0.95 [0.72; 1.21]	0.62 [0.43; 0.83]	0.47 [0.31; 0.66]
MacPherson 2004	6348	0.58 [0.41; 0.79]	1.86 [1.54; 2.21]	0.36 [0.23; 0.53]	4.69 [4.19; 5.23]	1.20 [0.94; 1.48]	0.87 [0.65; 1.11]	0.65 [0.46; 0.86]	0.17 [0.09; 0.29]	0.96 [0.74; 1.22]	0.38 [0.24; 0.54]
Melchart 2004	97733	4.56 [4.43; 4.70]	3.28 [3.17; 3.39]	0.18 [0.15; 0.20]	0.48 [0.44; 0.53]	0.12 [0.10; 0.14]					0.33 [0.29; 0.36]
Endres 2004	190924	5.18 [5.08; 5.28]	0.05 [0.04; 0.06]	24.51 [24.31; 24.70]	0.70 [0.67; 0.74]	1.31 [1.26; 1.36]		0.08 [0.07; 0.10]			0.07 [0.05; 0.08]
Witt 2009	229230	6.15 [6.05; 6.24]	0.45 [0.43; 0.48]	0.60 [0.57; 0.63]	0.30 [0.28; 0.33]	0.40 [0.38; 0.43]	0.26 [0.24; 0.28]	0.26 [0.24; 0.28]	0.76 [0.72; 0.79]	0.22 [0.20; 0.24]	0.11 [0.10; 0.12]
Weidenhammer 2008 therapists	503397	4.84 [4.78; 4.90]	3.95 [3.90; 4.01]	0.15 [0.14; 0.16]	0.08 [0.07; 0.08]	0.08 [0.07; 0.09]				0.01 [0.01; 0.02]	0.26 [0.25; 0.28]
Fixed effect		5.09 [5.05; 5.13]	1.81 [1.78; 1.84]	1.85 [1.83; 1.88]	0.25 [0.24; 0.26]	0.29 [0.28; 0.30]	0.28 [0.26; 0.31]	0.18 [0.17; 0.19]	0.74 [0.71; 0.77]	0.06 [0.05; 0.06]	0.19 [0.18; 0.20]
Random effect		4.67 [2.08; 8.22]	3.75 [0.74; 8.94]	2.79 [0.02; 10.01]	1.95 [0.40; 4.63]	1.48 [0.00; 5.90]	1.45 [0.07; 4.51]	0.69 [0.02; 2.34]	0.60 [0.21; 1.20]	0.60 [0.04; 1.81]	0.57 [0.01; 1.95]
tau^2		0.0008	0.0085	0.0494	0.0012	0.0017	0.0018	0.0004	0.0005	0.0008	0.0003
I^2		99.4% [99.3%; 99.5%]	99.9% [99.9%; 99.9%]	100.0% [100.0%; 100.0%]	99.7% [99.7%; 99.7%]	99.8% [99.8%; 99.8%]	96.3% [94.6%; 97.5%]	98.1% [97.4%; 98.7%]	92.6% [85.7%; 96.2%]	99.3% [99.1%; 99.4%]	99.0% [98.7%; 99.2%]
p-value Q-test		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Study	Total number of patients	Risk as patients with AE per 100 patients [95%-CI]								
		Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
List 1992	29			41,38 [24,41; 59,48]				20,69 [8,19; 37,03]		
Chung 2015	59	13.56 [6.0980; 23.38]			1,69 [0,00; 6,52]	0,00 [0,00; 1,62]				
Wen 2016	120									
Melchart 1998	121		0.83 [0.00; 3.21]				0,83 [0,00; 3,21]			
Leung 2009	254									
Yamashita 2000	391	0.51 [0.0485; 1.46]								
Ernst 2003	409	0.49 [0.0463; 1.40]	0.49 [0.05; 1.40]	0,24 [0,00; 0,96]			0,98 [0,26; 2,16]			0,24 [0,00; 0,96]
Zhao 2011	1968			0,10 [0,01; 0,29]						
Furuse 2017	2180	0.05 [0.0000; 0.18]				0,60 [0,32; 0,96]			0,96 [0,60; 1,42]	
Weidenhammer 2008 patients	5998	1.37 [1.0889; 1.68]	0.60 [0.42; 0.81]	0,35 [0,22; 0,52]				0,13 [0,06; 0,24]		0,07 [0,02; 0,15]
MacPherson 2004	6348	1.21 [0.9585; 1.50]				1,04 [0,81; 1,30]	1,24 [0,99; 1,53]	0,74 [0,54; 0,97]	0,44 [0,29; 0,62]	
Melchart 2004	97733	0.04 [0.0275; 0.05]				0,25 [0,22; 0,28]				
Endres 2004	190924					0,00 [0,00; 0,00]	0,04 [0,03; 0,05]	0,04 [0,03; 0,05]	0,00 [0,00; 0,00]	
Witt 2009	229230	0.52 [0.4944; 0.55]	0.27 [0.25; 0.29]	0,08 [0,07; 0,09]	0,09 [0,08; 0,10]	0,01 [0,00; 0,01]	0,09 [0,08; 0,11]	0,04 [0,03; 0,05]	0,01 [0,00; 0,01]	0,02 [0,01; 0,02]
Weidenhammer 2008 therapists	503397	0.03 [0.0287; 0.04]	0.42 [0.40; 0.43]			0,28 [0,27; 0,30]	, 0,0197 [0,02; 0,02]			
Fixed effect		0.12 [0.11; 0.13]		0,09 [0,08; 0,10]	0,09 [0,08; 0,10]	0,11 [0,11; 0,12]	0,04 [0,04; 0,04]	0,05 [0,04; 0,05]	0,00 [0,00; 0,01]	0,02 [0,01; 0,02]
Random effect		0.51 [0.03; 1.55]	0.40 [0.24; 0.61]	0,38 [0,00; 4,79]	0,35 [0,00; 35,67]	0,22 [0,01; 0,67]	0,20 [0,00; 0,81]	0,16 [0,00; 0,91]	0,14 [0,00; 1,16]	0,04 [0,00; 0,26]
tau²		0.0012	0.0001	0.0011	0.0029	0.0009	0.0002	0.0001	0.0002	0.0001
I²		99.6% [99.6%; 99.7%]	96.4% [93.9%; 97.9%]	94.6% [90.2%; 97.1%]	= 58.2% [0.0%; 90.1%]	99.7% [99.7%; 99.8%]	98.7% [98.2%; 99.1%]	97.1% [95.3%; 98.2%]	98.3% [97.3%; 99.0%]	69.0% [0.0%; 91.0%]
p-value Q-test		< 0.0001	< 0.0001	< 0.0001	0.1221	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0398

Online supplementary appendix S6: Risks for different types of adverse events per 100 patients undergoing an acupuncture series as reported in single studies

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses displayed in table 4

Study	Total number of treatments	Risk as treatments with AE per 100 treatments [95%-CI]									
		Bleeding	Pain	Other local AE	Vegetative nervous system	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal /gynaecologcial AE	Unclassified AE
Yamashita 2000	1441	45.45 [42.89; 48.03]	15.75 [13.92; 17.68]	0.90 [0.48; 1.46]	4.72 [3.69; 5.87]	1.11 [0.63; 1.72]	0.35 [0.11; 0.72]		0.07 [0.00; 0.27]		
daSilva 2014	13884	4.11 [3.79; 4.45]	3.02 [2.74; 3.31]	0.43 [0.33; 0.55]	0.02 [0.00; 0.05]		0.01 [0.00; 0.03]	0.11 [0.06; 0.17]		0.04 [0.01; 0.07]	
Melchart 1998	1200	0.33 [0.09; 0.74]	4.17 [3.11; 5.37]	0.17 [0.02; 0.48]	2.58 [1.76; 3.56]	1.75 [1.09; 2.57]	0.25 [0.05; 0.61]	0.08 [0.00; 0.33]	0.08 [0.00; 0.33]	0.42 [0.13; 0.86]	
MacPherson 2005	9408	4.72 [4.30; 5.16]	12.27 [11.61; 12.94]	0.26 [0.16; 0.37]	27.87 [26.97; 28.78]	1.75 [1.50; 2.03]		0.35 [0.24; 0.48]	4.49 [4.08; 4.91]	1.18 [0.97; 1.41]	0.35 [0.24; 0.48]
Furuse 2017	14039	3.16 [2.88; 3.46]	1.25 [1.07; 1.44]	0.09 [0.04; 0.14]	0.63 [0.51; 0.77]	0.20 [0.13; 0.28]	0.09 [0.05; 0.15]	0.07 [0.03; 0.12]		0.10 [0.05; 0.16]	0.20 [0.13; 0.28]
Ernst 2003	3535	5.18 [4.47; 5.93]	1.30 [0.95; 1.70]	0.08 [0.02; 0.21]	2.46 [1.98; 3.00]	0.25 [0.12; 0.45]	1.08 [0.76; 1.44]	1.44 [1.08; 1.86]		0.34 [0.17; 0.56]	5.46 [4.74; 6.23]
Odsberg 2001	9277	18.44 [17.66; 19.24]	0.08 [0.03; 0.14]	0.05 [0.02; 0.11]	1.42 [1.19; 1.67]	2.33 [2.03; 2.65]	0.18 [0.11; 0.28]	0.01 [0.00; 0.04]		0.02 [0.00; 0.06]	0.06 [0.02; 0.13]
Yamashita 1999	65482	0.03 [0.02; 0.05]	0.01 [0.00; 0.02]	0.00 [0.00; 0.01]	0.00 [0.00; 0.01]	0.00 [0.00; 0.01]	0.01 [0.00; 0.02]	0.00 [0.00; 0.01]		0.01 [0.00; 0.02]	0.00 [0.00; 0.01]
Park 2009	1095	8.40 [6.83; 10.12]	3.38 [2.39; 4.53]		3.11 [2.16; 4.21]		0.82 [0.37; 1.44]	1.46 [0.84; 2.26]			0.46 [0.14; 0.94]
Leung 2009	2000	0.40 [0.17; 0.72]									
Park 2010	3071	1.95 [1.49; 2.47]	0.49 [0.27; 0.77]	0.10 [0.02; 0.24]	0.75 [0.66; 0.85]	0.07 [0.01; 0.19]	0.03 [0.00; 0.13]	0.26 [0.11; 0.47]		0.03 [0.00; 0.13]	0.03 [0.00; 0.13]
White 2001	31822	3.09 [2.90; 3.28]	1.15 [1.04; 1.27]	0.10 [0.07; 0.13]	4.73 [4.50; 4.95]	0.98 [0.87; 1.09]	0.01 [0.00; 0.03]	0.00 [0.00; 0.01]		0.02 [0.01; 0.04]	0.46 [0.39; 0.54]
MacPherson 2001	34407	2.08 [1.93; 2.23]	1.24 [1.12; 1.35]	0.01 [0.00; 0.02]	4.73 [4.50; 4.95]	2.83 [2.66; 3.01]	0.63 [0.55; 0.71]		0.51 [0.44; 0.59]	0.31 [0.25; 0.37]	0.86 [0.76; 0.96]
Fixed effect		1.87 [1.80; 1.93]	0.82 [0.78; 0.87]	0.05 [0.04; 0.06]	1.08 [1.04; 1.13]	0.58 [0.55; 0.62]	0.09 [0.07; 0.10]	0.03 [0.02; 0.04]	0.96 [0.87; 1.05]	0.08 [0.07; 0.09]	0.23 [0.20; 0.25]
Random effect		4.92 [1.18; 11.01]	2.43 [0.63; 5.35]	0.13 [0.04; 0.27]	2.24 [0.21; 6.35]	0.84 [0.26; 1.75]	0.20 [0.05; 0.46]	0.19 [0.02; 0.55]	0.73 [0.00; 5.02]	0.15 [0.03; 0.38]	0.47 [0.03; 1.46]
tau^2		0.0169	0.0095	0.0004	0.0213	0.0055	0.0011	0.0008	0.0085	0.0008	0.0025
I^2		99.9% [99.9%; 99.9%]	99.8% [99.8%; 99.8%]	96.4% [94.9%; 97.4%]	99.9% [99.9%; 99.9%]	99.7% [99.6%; 99.7%]	98.4% [97.9%; 98.8%]	97.5% [96.6%; 98.2%]	99.5% [99.4%; 99.7%]	98.2% [97.6%; 98.6%]	99.4% [99.2%; 99.5%]
p-value Q-test		< 0.0001	< 0.0001	0.0001	< 0.0001	< 0.0001	0.0001	< 0.0001	0.0001	0.0001	0.0001

Study	Total number of treatments	Risk as treatments with AE per 100 treatments [95%-CI]								
		Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
Yamashita2000	1441	0.14 [0.01; 0.40]				0.62 [0.28; 1.10]				
daSilva2014	13884					0.24 [0.16; 0.33]				
Melchart1998	1200		0.08 [0.00; 0.33]				0.08 [0.00; 0.33]			
MacPherson2005	9408						0.67 [0.51; 0.84]			
Furuse2017	14039	0.01 [0.00; 0.03]	0.01 [0.00; 0.04]			0.10 [0.05; 0.16]			0.17 [0.11; 0.25]	
Ernst2003	3535	0.06 [0.01; 0.16]	0.06 [0.01; 0.16]	0.03 [0.00; 0.11]			0.11 [0.03; 0.25]			0.03 [0.00; 0.11]
Odsberg2001	9277	0.05 [0.02; 0.11]		0.01 [0.00; 0.04]			0.04 [0.01; 0.10]			
Yamashita1999	65482					0.04 [0.03; 0.06]	0.01 [0.00; 0.02]		0.01 [0.00; 0.02]	
Park2009	1095									
Leung2009	2000									
Park2010	3071	0.03 [0.00; 0.13]		0.10 [0.02; 0.24]		0.10 [0.02; 0.24]				
White2001	31822	0.11 [0.08; 0.15]		0.00 [0.00; 0.01]		0.15 [0.11; 0.19]	0.01 [0.00; 0.02]		0.00 [0.00; 0.01]	
MacPherson2001	34407	0.00 [0.00; 0.01]		0.00 [0.00; 0.01]		0.01 [0.00; 0.02]	0.01 [0.00; 0.03]		0.00 [0.00; 0.01]	
Fixed effect		0.03 [0.02; 0.05]	0.02 [0.01; 0.05]	0.01 [0.00; 0.01]		0.06 [0.05; 0.08]	0.03 [0.02; 0.03]		0.01 [0.01; 0.02]	
Random effect		0.04 [0.01; 0.10]	0.03 [0.00; 0.13]	0.01 [0.00; 0.04]		0.12 [0.02; 0.28]	0.08 [0.00; 0.27]		0.02 [0.00; 0.18]	0.03 [0.00; 0.11]
tau²		0.0002	0.0001	0.0001		0.0002	0.0004		0.0001	
I²		90.3% [82.5%; 94.6%]	21.2% [0.0%; 91.8%]	58.1% [0.0%; 84.4%]		95.1% [92.0%; 96.9%]	96.8% [95.1%; 97.9%]		95.0% [90.3%; 97.5%]	
p-value Q-test		0.0001	0.2811	0.0489		0.0001	0.0001		0.0001	

Online supplementary appendix S7: Risks for different types of adverse events per 100 treatments as reported in single studies

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses displayed in table 4

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Acupuncture related adverse events – systematic review and meta-analyses of prospective clinical studies

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Abstract

Objective

Overview on risks for acupuncture related adverse events (AE).

Design

Systematic review and meta-analysis of prospective studies.

Data sources

Pubmed, Scopus, and EMBASE from inception date to September 15, 2019.

Eligibility criteria for selecting studies

Prospective studies assessing AE caused by needle acupuncture in humans as primary outcome published in English or German

Data extraction and synthesis

Two independent researchers selected articles, extracted the data and assessed study quality. Overall risks and risks for different AE categories were obtained from random effects meta-analyses.

Main outcomes

Overall risk for minor AE and serious AE (SAE) per patients and per treatments

Results

A total of 7679 publications were identified. Twenty-two articles reporting on 21 studies were included. Meta-analyses suggest at least one AE occurring in 9.31% (95%-CI 5.10 to 14.62; 11 studies) of patients undergoing an acupuncture series and in 7.57% (95%-CI 1.43 to 17.95; 5 studies) of treatments. Summary risk estimates for SAE were 1.01 (95%-CI 0.23 to 2.33; 11 studies) per 10,000 patients and 7.98 (95%-CI 1.39 to 20.00; 14 studies) per 1 million treatments, for AE requiring treatment 1.14 (95%-CI 0.00 to 7.37; eight studies) per 1000 patients. Heterogeneity was substantial ($I^2 > 80\%$). On average 9.4 AE occurred in 100 treatments. Half of the AE were bleeding, pain, or flare at the needle site that are argued to represent intended acupuncture reaction. AE definitions and assessments varied largely.

Conclusion

Acupuncture can be considered among the safer treatments in medicine. SAE are rare, and most common minor AE are very mild. AE requiring medical management are uncommon but necessitate medical competence to assure patient safety. Clinical and methodological heterogeneity call for standardized AE assessments tools, clear criteria for differentiating acupuncture related AE from therapeutically desired reactions, and identification of patient related risk factors for AE.

PROSPERO registration number

CRD42020151930

Keywords

Adverse effects, adverse reactions, meta-analysis, safety, risk, pneumothorax

Strengths and limitations of this study

- First systematic review on acupuncture related adverse events including a risk of bias assessment
- First meta-analyses on adverse events related to acupuncture
- Complying with PRISMA guidelines
- Combining studies with heterogeneous AE definitions, but providing respective sensitivity analyses
- Causality assessment based on descriptions of adverse events as available from the included articles

Introduction

Acupuncture describes the insertion of fine needles at defined points on the patients' body for therapeutic or preventive purposes. It is used worldwide with growing popularity. In the EU acupuncture was identified as the most frequently provided method of complementary and alternative medicine (CAM) with 80,000 physicians and 16,380 non-medical practitioners.(1) In the UK alone 2.3 million traditional acupuncture treatments are carried each year.(2) In the US the number of acupuncturists doubled between 2002 and 2012.(3) The effectiveness of acupuncture is supported by level 1a evidence e.g. for chronic musculoskeletal pain and headache,(4-6) post-operative pain,(7, 8) post-operative nausea and vomiting,(9) as well as allergic rhinitis.(10) Furthermore, promising evidence exists for its potential role in the treatment of numerous other indications, such as stroke rehabilitation,(11) depression,(12) aromatase inhibitor induced arthralgia,(13) and asthma.(14) Thus, acupuncture offers a non-pharmacological treatment option for various highly prevalent conditions with great disease burden and significant health economic impact. Long-term pharmacological treatment of these conditions is often associated with substantial side effects.(15, 16) Consequently, also risk estimates on acupuncture related adverse events (AE) are required for evidence-based risk benefit considerations that are essential for clinical decision making.

However, uncertainty remains about acupuncture safety. AE related to acupuncture are repeatedly and controversially discussed both in scientific literature as well as in public media. An overview of systematic reviews in 2017 (17) illustrates that many of the previous reviews on the safety of acupuncture just summarized case reports or case series. In turn, those reviews including studies that do allow for AE frequency estimation, such as cohort studies and large RCTs, mostly only addressed certain types of AE, particular patient groups, restricted acupuncture regimens, or certain countries. These data are surely important for clinical decision making in particular cases, but leave the overall risk of acupuncture related AE in the general population obscure. Additionally, debate exists about differentiating AE from therapeutically intended reactions that are claimed to form part of the acupuncture treatment. For example, international consensus exists that aggravation of symptoms represents an AE, because disease burden increases. However,transient worsening of symptoms followed by long-term improvements can be interpreted as a so called healing crisis in complementary and alternative medicine.(18) In contrast, such consensus is still missing for local reactions, such as small bleedings upon needle withdrawal, needling pain, and flare around the needling site. These are also interpreted as beneficial signs by acupuncture experts and in standard text books and have been linked to neurophysiological mechanisms of acupuncture. Accordingly, quality and intensity of these events should be considered when classifying them as AE.(19-21)

The last review on prospective studies on AE related to acupuncture with high external validity dates back to 2001,(22) did not meta-analytically summarize AE risk estimates, and did not assess the quality of included studies. In addition, inconsistency and incompleteness of reporting in primary studies hampered the drawing of firm conclusions on acupuncture safety. Since then various large-scale clinical trials and nationwide surveys on acupuncture safety have been conducted.

Therefore, it was the aim of this review to provide an up to date summary of prospective trials that were particularly designed to evaluate AE related to needle acupuncture with manual or electrical stimulation and in combination with or without moxibustion.

Methods

We systematically reviewed prospective studies that reported on acupuncture related AE. The protocol has been registered at the International prospective register of systematic reviews (PROSPERO) (23) on September 25, 2019 (registration number CRD42020151930; online supplementary appendix S1). The research checklist according to the

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (24) and according to the guideline of Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (25) are displayed in the online supplementary appendix S2.

Search strategy

We searched Pubmed, Scopus, and EMBASE for articles published before September 15, 2019 by applying the following search strategy: 1: acupuncture; 2: “adverse event”; 3:”adverse events”; 4: “adverse effect”; 5: “adverse effects”; #1 AND #2; #1 AND #3; #1 AND #4; #1 AND #5. Additional records were identified from previous reviews on acupuncture related AE.(17) “Acupuncture” and “adverse effects” are MeSH terms.

In- and exclusion criteria

We included articles reporting on prospective studies (cohort studies, RCTs, surveys or surveillances) assessing AE associated with needle acupuncture involving manual or electrical stimulation combined with or without moxibustion in humans as their primary outcome. Case reports and case series were not included. Only articles published in English or German were included. Publications on assessments of acupuncture point injection therapies or non-penetrating acupuncture point stimulation, such as laser acupuncture, acupressure, or transcutaneous electrical nerve stimulation (TENS), were excluded. We also excluded articles reporting solely on moxibustion or restricted acupuncture regimens such as press-needle, auricular, or one-point acupuncture. Trials focusing just on one type of acupuncture related AE or just on a narrowly defined patient population were excluded.

Article selection and data extraction

Article selection was performed independently by two reviewers (WZ and PB, TS and PB, or LM and PB). Retrieved records were first screened for eligibility by abstract. Full texts were obtained for the remaining articles. Final decision about eligibility was obtained by consensus of all four reviewers.

Estimates of overall risks and risks for each reported type of AE were extracted as absolute numbers of patients with AE per total number of patients and treatments with AE per total number of treatments. Data concerning AE from sham- or placebo-acupuncture treatments were not extracted. The different types of AE were assigned to one of the following categories: bleeding, local pain, other local AE, distant pain, central nervous system, peripheral nervous system, vegetative nervous system, motor system, gastrointestinal / gynaecological system, cardiovascular system, respiratory system, generalized skin reactions, headache, emotional interference, sleeping problems, AE related to moxibustion, needling malpractice, aggravation of symptoms, other or unclassified AE (online supplementary appendix S3).

Following the differentiation between AE and adverse drug reactions (ADR) defined by the International Conference on Harmonization (ICH) of Good Clinical Practice,(26) articles were classified into reports on adverse events irrespective of their causal relationship to acupuncture and adverse reactions for which a causal relationship was a reasonable possibility. Serious adverse events (SAE) were reported as indicated in the included articles as in accordance with the ICH-criteria. These include any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.(26) AE definitions and severity assessments as stated in the included publications are provided in the online supplementary appendix S4. Causality assessment of SAE was performed by independent acupuncture therapists who were medical doctors who received more than 300 hours of acupuncture training and with more than ten years of intensive acupuncture practice. As the basis of this assessment was limited to incomplete information provided in the articles, lacking e.g. time references, the standard

categories of the WHO-UMC causality assessment system (27) were reduced to possibly related to acupucture,unlikely related to acupuncture, or unclassifiable. AE risk estimates given as patients with AE per total number of patients were interpreted according to the guidelines of the Council for International Organizations of Medical Sciences (CIOMS) as very common (≥ 1/10 patients), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000).(28)

Documentation of study characteristics included the study type, the country in which the study was conducted, the reporter, the method and the time point of AE assessment, complaints as well as the age and the gender structure of the study population, the average number and the frequency of treatments per patient, the average number of needles per treatment, the needle in time, the acupuncture style, the method of needle stimulation, and the number, the gender, the training, and years of experience of acupuncturists. Data on patients' and acupuncturists' AE reports from the article published by Weidenhammer et al. in 2008 were handled as two separate trials.

Risk of bias assessment

Included studies were assessed for risk of bias according to a checklist developed by Faillie and colleagues for systematic reviews focusing on drug adverse events.(29) This checklist is applicable to RCTS, cohort studies, case-control studies, nested case-control studies, and systematic reviews. The questions are structured in eight risk of bias domains. Possible answers are "Not applicable" (n/a), "Yes" (Y), "Unclear" (U), or "No" (N). A summary risk of bias assessment is provided for each domain as well as for the whole study. According to the inclusion criteria of this review, questions concerning systematic reviews, cross-over trials, and case-control studies were not applicable.

Data analysis

Data were analysed using the package meta implemented in R.(30) Pooled estimates with 95% confidence intervals (CI) for overall AE risk and risks of different types of AE were obtained from proportion meta-analyses. Random effects models were calculated by the Hartung-Knapp method with arcsine transformation of proportions. Cochran Q test, and I^2 statistics were used to assess the heterogeneity of included studies. Meta-analyses were performed for the overall risks for an AE, for SAE, for AE requiring treatment, and the risks for the different types of AE. Separate meta-analyses were conducted for AE risks given as the number of patients with AE per total number of patients undergoing an acupuncture series and AE risks given as the number of treatments with AE per total number of treatments performed. All studies reporting the respective risks were included in the different meta-analyses. All AE that were reported separately in the articles, but that were allocated to the same AE category, were treated as they had occurred in different patients or treatments, respectively. Sensitivity analyses were performed for studies that explicitly only reported about AE that had, at the discretion of the assessors', a causal relationship to acupuncture treatments. None of the articles reported the mean and variance of the number of AE per treatment. Thus, the expected number of AE per treatment could not be estimated by means of a meta-analysis but just by considering the sum of AE relative to the sum of treatments. An additional sensitivity analysis was performed by excluding AE that are usually very mild and transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point. AE of such type that were indicated by any means as significant were not excluded from this sensitivity analysis.

Patient and public involvement

No patients were involved in defining the research question, the outcome measures, the design, or conduct of this review. No patients were asked to advise on interpretation of results. Authors will share the results during patient seminars and information events. A concise version of the results will be made available for non-profit acupuncture organisations to be presented on their webpages.

Results

Study characteristics

7677 records were retrieved from the database search and two were identified from previous reviews on acupuncture related adverse events. 7499 records could be screened by abstract and for 180 articles full-texts were obtained. A total of 22 articles reporting on 21 studies covering 12.9 million treatments met our inclusion criteria (Figure 1).(31-52) In two studies different data assessments on different subpopulations were performed and are treated independently in the present analyses. In one study patient reported AE were assessed after one of the first treatments and three months after treatment,(38, 39) and in one large study AE were documented by therapists and in addition by a subgroup of patients.(46)

Study characteristics are provided in table 1. The four largest trials, which included 100,000 to 500,000 patients treated in over 750,000 acupuncture sessions, were cohort studies performed as part of the German Model Projects on Acupuncture (*Modellvorhaben Akupunktur*).(33, 41, 46, 49) Three nationwide surveys from the UK (described in four articles),(38-40, 48) one in-house surveillance report from Japan,(51) and one summary of AE assessments nested within three Chinese RCTs (52) included two to six thousand patients receiving over 30 thousand treatments, respectively. In three surveys, two from South-Korea,(44, 45) one from Japan, (35) and one from Brazil,(32) around one to two thousand patients were included and treated in up to 14 thousand acupuncture sessions. One nationwide survey conducted in Sweden reported on the risk of AE based on data from over nine thousand acupuncture sessions.(43) In seven studies less than 500 patients receiving a maximum of 3.5 thousand treatments were included; four AE assessments nested within RCTs or clinical trials from China,(36, 47) Hong-Kong,(31) and Sweden,(37) one Japanese (50) and one German survey (34) as well as one German cohort study.(42) In most studies acupuncture was used to treat pain in middle aged patients. In six articles no details on the patients' condition were provided.(34, 35, 40, 43, 48, 50) Two articles reported explicitly on short-term AE after one particular treatment only.(39, 45) All but five articles provided sufficient information to infer that acupuncturists had a firm medical background and / or had received intensive acupuncture training.(34, 36, 37, 42, 43) One German survey also included "other practitioners" most likely non-medical practitioners (*Heilpraktiker*) with non-standardized acupuncture training.(34)

Eight articles described AE reported by patients only (31, 32, 37-39, 45, 46, 49) and seven articles AE reported by acupuncturists only.(33, 40, 41, 44, 46, 48, 51) As before said Weidenhammer et al. described therapists' and patients' reports on AE separately.(46) Zhao et al. combined the AE reports from patients and acupuncturists.(52) In five articles it was explicitly stated that acupuncturists recording the AE also queried their patients about any uncomfortable experience during or after treatment.(34-36, 43, 50) In two trials AE were documented by an independent assessor.(42, 47) In eight of the 22 included articles AE were reported irrespective of their relationship to acupuncture,(31, 33, 34, 37, 40, 48, 51, 52) while descriptions of AE assessments in twelve articles suggest that only AE related to the acupuncture treatment were documented,(32, 35, 36, 38, 39, 42-44, 46, 49, 50) and one article did not provide information about the AE definition.(45) Further discrepancies were found in definitions of certain reactions as therapeutically intended. For example, da Silva et al. did not count aggravation of symptoms as AE, because of difficulties in determining causality as well as severity and because of common notion among practitioners that transient worsening forms part of the acupuncture treatment.(32) In contrast White et al. reported observations of aggravated symptoms as AE, but only those that were not followed by substantial improvements.(48) In contrast, the other articles did not specify aggravation of symptoms further.(33-35, 37, 38, 42, 46, 49, 50) In addition, Endres et al. did report on erythema at the needling site (which was accounted for in the present analysis), but did not include it in their overall AE incidence report, as this can also be regarded as desired acupuncture reaction.(33)

1st Author year	Country	Study type	Patients			Treatments				Acupuncturists				AE assessment		
			n total (female)	Age [a]	Indication	n (total)	n / patient	n needles	Stimulation	n total (n female)	Medical background	Acupuncture training	Acupuncture practice	Reporter	Tool	Time point
Chung 2015	Hong-Kong	RCT	59 (46)*)	49 ± 10*)	Insomnia in major depressive disorder	531	9 / 3 w	14	EA	n.i.	TCM doctors	n.i.	> 3 a	P	SL & OQ any AE	after 3rd, 6th, 9th treatment
da Silva 2014	Brazil	Cohort monocentric	1157 (n.i.)	n.i.	Musculoskeletal, emotional &respiratory disorders i.a.	13,884	12#)	n.i.	MA	n.i.	MD	in training	n.i.	P	SL & OQ AE related to acu.	after each treatment
Endres 2004	Germany	Cohort nationwide private clinics	190,924 (130,974)	f: 58 ± 16 m: 55 ± 15	Chronic headache, LBP or arthrosis (> 6 m)	1.77 M	apx. 10 / 4 - 8 w	n.i.	n.i.	12,000 (n.i.)	MD	> 140 h	n.i.	A	SL & OQ any AE	after last treatment
Ernst 2003	Germany	Survey private practices	409 (279)	n.i.	n.i.	3,535	f: 9.0 m: 7.9	n.i.	n.i.	29 (n.i.)	MD & other practitioners	n.i.	n.i.	A also asking P	SL & OQ any AE	after each treatment; at subsequent visit
Furuse 2017	Japan	Survey 8 acupuncture clinics	2180 (1288)	54 ± 19	n.i.	14,039	6.4#	n.i.	MA, EA & Moxa	232 (93)	Japanese lic. acupuncturists	> 3 a	9 ± 10 a	A also asking P	SL AE related to acu.	after each treatment; at subsequent visit
Leung 2009	Hong-Kong	11 clinical trials (not specified)	254 (n.i.)	n.i.	Chronic pain, neurological & urological conditions	2,000	n.i.	5 avg.	MA & EA	2 (n.i.)	TCM doctors	n.i.	n.i.	A also asking P	SL AE related to acu.	after each treatment & subsequent visit
List 1992	Sweden	RCT monocentric	29 (n.i.)	median 40**)	Craniomandibular disorder	apx. 174	≥ 6 / 6 - 8 w	12 avg.	MA & EA	1 (0)	n.i.	n.i.	n.i.	P	SL & OQ any AE	after last treatment
MacPherson 2001	UK	Survey nationwide private practices	n.i.	n.i.	n.i.	34,407	n.i.	1 - 20	n.i.	574 (374)	MD & physio-therapists	1 – 2 a 11% ≥ 3 a 89%	< 10 a apx. 60% ≥ 10 a apx. 40%	A	SL & OQ any AE	upon recognition
MacPherson 2004 A	UK	Survey nationwide private practices	6,348 (4,821)	52 ± 15	Musculoskeletal, psychological, general, neurological, gyne-cological, obstetric & respiratory conditions; wellbeing	30,196	4.8	n.i.	MA & EA	638 (406)	MD & physio-therapists	> 3 a	< 10 a 58% ≥ 10 a 42%	P	SL & OQ AE related to acu.	3 m after inclusion
MacPherson 2005 A			9,408 (6,961)	51		9,408	1								SL imm. AE AE related to acu.	After the 1st / one of the 1st treatments
Melchart 1998	Germany	Cohort monocentric	121 (88)	54 ± 13	Mainly chronic pain	apx. 1,200	9.9 ± 4.7	n.i.	n.i.	n.i.	TCM doctors	n.i.	n.i.	Independent A asking P	SL & FT AE related to acu.	at subsequent visit
Melchart 2004	Germany	Cohort nationwide private clinics	97,733 (78,675)	55 ± 16	Chronic headache, osteoarthritis, LBP	apx. 760,000	7.8 ± 2.4	12.6 ± 5.1	n.i.	7050 (n.i.)	MD	> 140 h (19% > 350 h)	n.i.	A	SL & FT AE related to acu.	after last treatment
Odsberg 2001	Sweden	Survey private practices	n.i.	n.i.	n.i.	9,277	n.i.	n.i.	MA & EA	187 (n.i.)	Physio-therapists	n.i.	n.i.	A also asking P	n.i. AE related to acu.	after each treatment
Park 2009	South-Korea	Survey two-centred	1,095 (696)	58 ± 13	Stroke, headache, hyper-tension, dizziness, i.a.	1,095	1	n.i.	n.i.	8 (n.i.)	Korean medicine doctor	n.i.	>10a	P	n.i.	after 1 arbitrary treatment
Park 2010	South-Korea	Survey private practices	2,226 (n.i.)	n.i.	n.i. (patients with AE mainly pain conditions)	3,071	1.4 / ≤ 5 w#)	n.i.	n.i.	13 (n.i.)	Oriental medicine.	6 a	< 3a 70% ≥ 3a 30%	A	SL AE related to acu.	upon recognition
Weiden-hammer 2008 B	Germany	Cohort nationwide private clinics	503,397 (40,5235)	54 ± 16	Chronic headache, LBP, osteoarthrosis (> 6 m)	4.2 M	8.4 (2.9)	n.i.	n.i.	9918 (3570)	MD	140 h (22% > 350 h)	n.i.	A	SL & FT AE related to acu.	after last treatment
			882847 (n.i.)	n.i.		7.9 M	n.i.								OQ - SAE only AE related to acu.	upon recognition
			5,998 (5,072)	55 ± 15		apx. 51582#)	8.6 (3.0)			9429 (n.i.)				P	OQ AE related to acu.	after last treatment
Wen 2016	China	RCT monocentric	120 (84)	59 ± 7	Posterior circulation ischemia	1,680	14 / 3 - 4 w	≤ 9	MA	1 (n.i.)	n.i.	n.i.	> 20 a	Blinded assessor	n.i. AE related to acu.	after each treatment
White 2001	UK	Survey private practices	n.i.	n.i.	n.i.	31,822	n.i.	n.i.	n.i.	78 (29)***)	MD & physio-therapists	≤ 100 h 43% > 100 h 57%	≤ 10 a 65% > 10 a 35%	A	SL & OQ any AE	upon recognition
Witt 2009	Germany	Cohort nationwide private clinics	229,230 (148,541)	51 ± 14	Chronic headache, osteo-arthritis, LBP, all. rhinitis, asthma, dysmenorrhea	2.2 M	10.2 ± 3.0	n.i.	n.i.	13579 (5418)	MD	> 140 h (15% > 350h)	6.9 ± 5.3 a	P	OQ AE related to acu.	after last treatment
Yamashita 1999	Japan	In-house surveillance	5,008 (2,804)	Mostly 40 - 50 a	Musculoskeletal disorder, miscellaneous complaints	65,482	13 avg.	n.i.	MA, EA & Moxa	84 (n.i.)	Japanese lic. acupuncturists	> 3 a	< 1 a 64% ≥ 1 a 36%	A	OQ any AE	upon recognition
Yamashita 2000	Japan	Survey monocentric	391 (n.i.)	12 - 88	n.i.	1,441	3.7#)	21#)	MA & EA	7 (n.i.)	Japanese lic. acupuncturists	> 3 a	n.i.	A also asking P	OQ AE related to acu.	after each treatment; at subsequent visit
Zhao 2011	China	3 RCTs multicenter	1,968 (1,239)	39 ± 14	Migraine, dyspepsia, Bell's palsy	39,360	20 / 4 w	2 - 5	MA & EA	n.i.	TCM doctors	≥ 8 a	> 10 a	P & A	SL & OQ any AE	after each treatment & after last treatment

Table 1: Study characteristics

AE: adverse event; SAE: serious adverse event; acu: acupuncture; MA: manual acupuncture; EA: electroacupuncture; Moxa: moxibustion; m: male, f: female; LBP: low back pain; MD: medical doctors; lic.: licensed; TCM: Traditional Chinese Medicine; SL: selection list; OQ: open questions, FT: free text; P: patients; A: acupuncturists; imm.: immediate; X ± X: mean ± standard deviation; a: year; w: weeks; h: hours; M: million; avg.: on average; i.a. inter alia; apx.: approximately; n.i.: not indicated; A) overlapping study populations from the same survey B) reports of patients and therapists separately presented; *) including one drop out prior to treatment; **) refers to total study population (n=61); ***) further professional details only provided by 59 acupuncturists; #) approximation based on other reported data

Risk of bias assessment

According to the inclusion criteria the study objective was clearly described in all articles (Figure 2, category A). Study design was clear for all but one article which stated that data were collected in the course of 11 clinical trials without further specification.(36) Furthermore, all but one AE assessment were free of a run in period. In one RCT the safety assessment was initiated with a short delay.(37) Both irregularities were rated as unlikely to introduce bias into the AE documentation. High risk for selection bias (Figure 2, category B) was identified in the four RCTs and the AE assessment in 11 clinical trials (23% of articles), due to exclusion of patients with comorbidities or bleeding tendency. In contrast, in all surveys and cohort studies (77%) the risk for selection bias was rated as unclear due to an indistinct selection of therapists and / or patients, inclusion of voluntarily participating acupuncturists or acupuncturists from specialized medical centres only. Furthermore, none of the articles stated that patients were naive to acupuncture. Risk of bias due to study withdrawal or drop-out (Figure 2, category C) was rated as low for all RCTs and two surveys, that only reported on short-term AE (27%), (39, 45) and as high for one survey (5%), because treatment was ceased for 40% of the patients with AE.(44) For the remaining studies (68%) the risk of bias due to early treatment termination was rated as unclear, as withdrawals and drop-outs due to AE were not reported. The risk of information bias regarding the safety outcome (Figure 2, category D) was rated as high for one study (5%) because of an exclusive documentation of repeatedly occurring AE (37) and as unclear for all remaining studies (95%). At this, AE reporting by patients or acupuncturists instead of an independent assessor was classified as an unclear risk for social desirability bias. Further possible but unclear sources of detection bias were the sole use of a selection list (35, 36, 39, 44) or the sole use of open questions as AE assessment tool,(49-51) lack of reporting on the AE assessment tool (43, 45, 47), unclear definition of the safety outcome, and the time-point of the AE assessment (only directly after treatment,(32, 33, 43, 47) only after the last treatment initiation,(37, 38, 41, 46, 49) solely upon recognition (40, 44, 48, 51)). Further risk of information bias (Figure 2, category E) appeared to be unclear due to poor reporting of treatment details in all but seven studies (32%).(31, 37, 40, 41, 47, 50, 52) Bias arising from differential care, confounder assessment, and statistical methods to control for confounding (Figure 2, category F) was rated as low, as crude AE risk estimates and not relative risks with respect to a comparator group were extracted. The risk of bias due to other statistical methods (Figure 2, category G) was also rated as low, as reporting of AE incidence was clear and well-structured in all articles.

Bias due to conflict of interest (Figure 2, category H) might be present in four articles (18%) due to funding by institutions with direct interest in the public acknowledgement of acupuncture.(38, 39, 43, 44) In eight articles (36%) funding or other conflicts of interest were not described.(34, 36, 37, 40, 42, 48, 50, 51) The ten remaining articles (45%) included an explicit statement about funding by independent institutions and the absence of other conflicts of interest. For all studies the overall risk of bias was rated as unclear based on the large proportion of unclear sources of bias.

Overall risk of acupuncture related adverse events

Eleven studies including 845,637 patients that assessed the overall AE risk as patients with AE among the total number of patients undergoing an acupuncture series were combined in a meta-analysis. The overall risk for at least one AE during a series of acupuncture treatments was estimated to be 9.31 (95%-CI 5.10 to 14.62) per 100 patients treated (Figure 3A). (31, 34, 36, 38, 41, 42, 46, 47, 49, 52) The median number of treatments per patient was 9 (min 4.8; max 14), and the total number of treatments exceeded 7.4 million. Visual inspection neither indicated an association of the incidence of AE with the number of treatments per acupuncture series nor with the study type (online supplementary appendix S5). Five studies reported the total number of acupuncture treatments with AE relative to the total number of treatments performed.(32, 34, 36, 40, 42) Meta-analysis of these studies covering 55,026 treatments in total

resulted in a risk of 7.57 (95%-CI 1.43 to 17.95) treatments with AE per 100 treatments (Figure 3B). Sensitivity analysis of studies reporting on adverse acupuncture reactions and not on AE irrespective of their relationship to acupuncture treatments resulted in similar estimates (32, 36, 38, 40, 41, 46, 47, 49); 8.23 (95%-CI 6.42 to 10.25) patients with at least one AE out of 100 patients (Figure 3C) and 6.08 (95%-CI 0.00 to 38.76) treatment with AE out of 100 treatments (Figure 3D). Heterogeneity for all meta-analyses mentioned above (including the sensitivity analyses) was substantial as indicated by an I^2 between 98% and 100% ($p < 0.01$).

Thirteen articles reported the incidences of different types of AE per treatment (table 2).(32, 34-36, 39, 40, 42-45, 48, 50, 51) The average number of AE per 100 treatments varied between 0.14 and 69.12. In total 18,002 AE were reported in of 190,661 treatments, which makes on average 9.44 AE per 100 treatments. Exclusion of AE that are usually mild and transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point, reduced this number to 4.81 (min - max 0.10 – 36.92) AE per 100 treatments.

Study	Number of treatments	Number of AE		AE incidence per 100 treatments		Bleeding, pain, flare at needling site as % of all AE
		total	excluding bleeding, pain & flare	total	excluding bleeding, pain & flare	
Park 2009	1095	193	64	17.63	5.84	66.84%
Ernst 2003	3535	632	403	17.88	11.40	36.23%
Melchart 1998	1200	120	66	10.00	5.50	45.00%
Yamashita 1999	65482	94	67	0.14	0.10	28.72%
Yamashita 2000	1441	996	114	69.12	7.91	88.55%
MacPherson 2001	34407	4544	3406	13.21	9.90	25.04%
Odsberg 2001	9277	2108	390	22.72	4.20	81.50%
White 2001	31822	2176	820	6.84	2.58	62.32%
MacPherson 2005	9408	5071	3473	53.90	36.92	31.51%
Leung 2009	2000	8	0	0.40	0.00	100.00%
Park 2010	3071	99	26	3.22	0.85	73.74%
da Silva 2014	13884	1107	117	7.97	0.84	89.43%
Furuse 2017	14039	854	232	6.08	1.65	72.83%
Overall	190661	18002	9178	9.44	4.81	49.02%

Table 2: Number of adverse events (AE) per treatment

Serious acupuncture related adverse events

SAE were observed in five studies including 1,182,860 patients undergoing 10,570,678 treatments with incidences between two and 40 SAE in 100,000 patients undergoing a treatment series and between two and 99 in one million treatments, respectively.(33, 38, 41, 46, 51) Four articles reported that none of the AE observed in a total of 1,922 patients undergoing 19,005 treatments required medical treatment,(32, 36, 47, 50) and authors of five articles concluded that none of the AE observed in 122,699 treatments fulfilled the ICH-criteria for SAE.(35, 40, 44, 48, 52) Eight articles did not mention SAE or any AE description that allowed for inferences about SAE.(31, 34, 37, 39, 42, 43, 45, 49)

Meta-analyses of the overall risk for a SAE resulted in 1.01 (95%-CI 0.23 to 2.33) patients with SAE in 10,000 patients undergoing an acupuncture series (Figure 4A, 11 studies 1,188,930 patients) and 7.98 (95%-CI 1.39 to 20.00) SAE in one million treatments (Figure 4B, 14 studies 10,712,382 treatments). Exclusion of studies with zero SAE incidences

changed these estimates to 1.47 (95%-CI 0.10 to 4.46) in 10,000 patients suffering from a SAE when undergoing an acupuncture series and 16.90 (95%-CI 0.49 to 56.60) in one million treatments causing an SAE. Sensitivity analyses of studies that only reported reactions with a plausible relationship to acupuncture resulted in risk estimates of 0.45 (95%-CI 0.06. to 1.18) SAE per 10,000 patients (Figure 4C) and 5.45 (95%-CI 0.50 to 15.67) per one million treatments (Figure 4D). Again, heterogeneity between studies included in these two meta-analyses was substantial ($I^2 > 85\%$, $p < 0.001$).

The causality assessment of the 73 SAE conducted by two acupuncture experts (table 3) resulted in 32 SAE (44%) being possibly related to acupuncture. Among those, pneumothorax, strong cardiovascular or vasovagal reactions, and fall or trauma were the most frequent SAE with a frequency of one to three cases in one million treatments each. One article that was not taken into account in the SAE meta-analyses, because observed AE were not categorized in minor AE and SAE, also reported two cases of pneumothorax in over 200,000 patients receiving on average 10 acupuncture treatments.(49) One of the included trials documented deaths occurring in the study population. Nineteen SAE (26%) were rated as unlikely related to acupuncture. Among those were nine deaths observed in one study in patients of an age between 67 and 87 years and related to a pre-existing health conditions.(33) Authors reported that the resulting death rate of 4.71 per 100,000 patients was below the expected death rate derived from population statistics. Other SAE classified as unlikely related to acupuncture were a circulatory reaction with amnesia, suicidal tendencies, acute general infection, a car crash two days after treatment, a malignant parotid tumour, tonic-clonic seizures, and an ophistotonus. Twenty-two SAE (30%), intervertebral disk prolapses and hospitalizations due to pain exacerbation or unknown reasons, were rated as “unclassifiable”.

Endres 2004	**Causality**	**n**
- Death	unlikely	9
- Fall or trauma, with or without fracture	possible	4
- Acute general infection with hospitalization	unlikely	2
- Allergic reaction to concomitant medication (atopy)	possible	1
- Stroke with hospitalization	unlikely	3
- Cardiovascular problems (hospital admission)	possible	3
- Intervertebral disk prolapse, pain exacerbation with hospital admission	unclassifiable	5
- Malignant parotid tumor (hospital admission)	unlikely	1
- Hospitalization (unknown reasons)	unclassifiable	17

Melchart 2004	**Causality**	**n**
- Exacerbation of depression	possible	1
- Hypertensive crisis	possible	1
- Vasovagal reaction	possible	1
- Asthma attack with hypertension and angina	possible	1
- Pneumothorax	possible	2

Yamashita 1999	**Causality**	**n**
- Hospitalization of patient with asthma because of coughing	possible	1
- 1 case of deep burn that recovered after 2 years	possible	1

Weidenhammer 2008 ther.	**Causality**	**n**
- Pneumothorax	possible	5
- Suicidiation in a patient with borderline syndrome	unlikely	1
- Hypertensive crisis	possible	1
- Syncope (vasovagal reaction)	possible	2
- Asthma attack in a patient with asthma	possible	1
- Erysipelas (one in a patient with lymphedema)	possible	2
- Circulatory collapse (one with uncontrolled defecation and one with vertigo and paresthesia)	possible	2
- Circulatory reaction with amnesia	unlikely	1
- Tonic-clonic seizures and ophistotonus	unlikely	1
- Infection of the knee joint with E. coli bacteria	possible	1

MacPherson 2004	**Causality**	**n**
- Low back pain in breast cancer patient, hospital admission, disappeared without medication, since then no more LBP	possible	1
- Car crash 2d after acupuncture, very little sleep the night before	unlikely	1
- Skin rash and feeling ill for several weeks accompanied by decrease of ME symptoms and feeling of catharsis (no treatment)	possible	1

Table 3: Causality assessment of serious adverse events as reported in included articles

The total number of serious adverse events (SAE) as well as the total number of treatments in each study can be identified from figure 4.

Acupuncture related adverse events requiring treatment

Eight studies determining the number of patients with AE requiring treatment during an acupuncture series included 1,211,791 patients. The meta-analysis of these studies yielded a summary estimate of 1.14 (95%-CI 0.00 to 7.37) in 1000 patients for the risk to suffer from an AE that required treatment when undergoing an acupuncture series (Figure 5). (31, 32, 36, 41, 46, 47, 49, 50) Also here, heterogeneity was substantial (I^2 100%). Two articles, that had defined AE requiring treatment as an SAE criterion, reported lower incidences (two and six events per 100,000 patients) (41, 46) than other two articles, reporting on AE requiring treatment without referring to SAE (1.7 and 2.2 in 100 patients).(31, 49)

Risk of different types of minor adverse events

Overall risk for the different types of minor AE (categorization see online supplementary appendix S3) were estimated in separated meta-analyses as patients with AE per total number of patients undergoing a treatment series or as treatments with AE per total number of treatments (Table 4). Risks estimated in single studies (online supplementary appendix S6 and S7) varied largely for all types of minor AE. Most frequent and commonly occurring minor AE with summary risk estimates between 1% and 5% of patients undergoing an acupuncture series were bleeding events, pain at the needling site, other local AE, vegetative reactions, aggravation of symptoms, and events related to the central nervous system. Summary risk estimates for bleeding events, needle site pain, vegetative reactions, and aggravation of symptoms also ranged from 1% to 5% of treatments, while meta-analysis of symptoms related to the central nervous system per acupuncture treatment resulted in a risk of two in 1000 treatments. AE estimated to be uncommon with summary risk estimates of one to seven out of 1000 patients undergoing an acupuncture series were symptoms of the peripheral nervous system, pain distant to the needling site, gastrointestinal or gynaecological symptoms, headache, cardiovascular symptoms, affection of the motor system, generalized skin reactions, adverse emotional reactions, and sleeping problems. Symptoms affecting the peripheral nervous system, distant pain, as well as gastrointestinal or gynaecological symptoms were estimated to occur in one to seven out of 1000 treatments; headache, cardiovascular, and motor symptoms as well as adverse emotional reactions only in one to eight out of 10,000 treatments. The risk for respiratory AE was estimated to be rare with a summary risk estimate of four out of 10,000 patients undergoing an acupuncture series and three out of 10,000 treatments. Summary risk estimates for AE caused by therapists' malpractice and burns caused by moxibustion were one to two in 1000 patients undergoing an acupuncture series and two in 10,000 to one in 1000 treatments, respectively.

Some of the studies showed outlying incidences for particular types of minor AE. List et al. observed at least one vegetative reaction in the course of an acupuncture series for craniomandibular disorder in over half of the patients (58.6%),(37) and MacPherson et al. reported vegetative reactions after over a quarter of treatments (27.9%).(39) These findings exceed the frequency of vegetative reactions of up to 13.6% of patients identified in the remaining studies and was mainly based on patient reports of abnormal tiredness after treatment. List et al. also report the highest incidence of aggravation of symptoms with 93% of CMD patients as well as the highest frequency of needle site pain with 44.8 % of patients. This was followed by an RCT with 32.2% of patients suffering needle site pain (31) and a cohort study among chronic pain patients of which 10% suffered aggravation of symptoms after receiving acupuncture.(42) The remaining 19 articles reported incidences smaller than 3% for aggravation of symptoms and 14% for needle site pain.

Type of AE	Number of studies	Sum of patients	Risk as patients with AE per 100 patients [95%-CI] overall	min	max	Tau² I²	Number of studies	Sum of treatments	Risk as treatments with AE per 100 treatments [95%-CI] overall	min	max	Tau² I²
Bleeding	13	1038741	4.67 [2.08; 8.22]	0.48 [0.32; 0.67]	25.18 [21.10; 29.50]	0.0008 99.4%**	13	190661	4.92 [1.18; 11.01]	0.03 [0.02; 0.05]	45.45 [42.89; 48.03]	0.0169 99.9%**
Needle site pain	14	1038907	3.75 [0.74; 8.94]	0.05 [0.04; 0.06]	44.83 [27.46; 62.87]	0.0085 99.9%**	12	188661	2.43 [0.63; 5.35]	0.01 [0.00; 0.02]	15.75 [13.92; 17.68]	0.0095 99.8%**
Other local AE	10	1034610	2.79 [0.02; 10.01]	0.15 [0.14; 0.16]	35.59 [23.97; 48.14]	0.0494 100.0%*	11	187566	0.13 [0.04; 0.27]	0.00 [0.00; 0.01]	0.90 [0.48; 1.46]	0.0004 96.4%**
Vegetative reaction	12	1036607	1.95 [0.40; 4.63]	0.08 [0.07; 0.08]	58.62 [40.52; 75.59]	0.0012 99.7%**	12	188661	2.24 [0.21; 6.35]	0.00 [0.00; 0.01]	27.87 [26.97; 28.78]	0.0213 99.9%**
Aggravation of symptoms	11	1036760	1.48 [0.00; 5.90]	0.08 [0.07; 0.09]	93.10 [81.26; 99.30]	0.0017 99.8%**	10	173682	0.84 [0.26; 1.75]	0.00 [0.00; 0.01]	2.83 [2.66; 3.01]	0.0055 99.7%**
Central nervous system	9	244553	1.45 [0.07; 4.51]	0.05 [0.00; 0.20]	37.93 [21.45; 55.99]	0.0018 96.3%**	11	179253	0.20 [0.05; 0.46]	0.01 [0.00; 0.02]	1.08 [0.76; 1.44]	0.0011 98.4%**
Peripheral nervous system	8	433118	0.69 [0.02; 2.34]	0.08 [0.07; 0.10]	27.59 [13.14; 44.96]	0.0004 98.1%**	10	152813	0.19 [0.02; 0.55]	0.00 [0.00; 0.01]	1.46 [0.84; 2.26]	0.0008 98.0%**
Distant pain	5	241817	0.60 [0.21; 1.20]	0.17 [0.09; 0.29]	0.95 [0.72; 1.21]	0.0005 92.6%**	4	46456	0.73 [0.00; 5.02]	0.07 [0.00; 0.27]	4.49 [4.08; 4.91]	0.0085 99.5%**
Gastrointestinal / gynaecologcial system	9	747559	0.60 [0.04; 1.81]	0.01 [0.01; 0.02]	17.24 [5.94; 32.83]	0.0008 99.3%**	10	186125	0.15 [0.03; 0.38]	0.01 [0.00; 0.02]	1.18 [0.97; 1.41]	0.0008 98.2%**
Unclassified AE	10	1036307	0.57 [0.01; 1.95]	0.07 [0.05; 0.08]	17.85 [14.29; 21.70]	0.0003 99.0%**	9	172136	0.47 [0.03; 1.46]	0.00 [0.00; 0.01]	5.46 [4.74; 6.23]	0.0025 99.4%**
Headache	9	845745	0.51 [0.03; 1.55]	0.03 [0.03; 0.04]	13.56 [6.10; 23.38]	0.0012 99.6%**	7	97592	0.04 [0.01; 0.10]	0.00 [0.00; 0.01]	0.14 [0.01; 0.40]	0.0002 90.3%**
Cardiovascular system	5	739155	0.40 [0.24; 0.61]	0.27 [0.25; 0.29]	0.83 [0.00; 3.21]	0.0001 96.4%**	3	18774	0.03 [0.00; 0.13]	0.01 [0.00; 0.04]	0.08 [0.00; 0.33]	0.0001 21.2%
Motor system	5	237634	0.38 [0.00; 4.79]	0.08 [0.07; 0.09]	41.38 [24.41; 59.48]	0.0011 94.6%**	5	82112	0.01 [0.00; 0.04]	0.00 [0.00; 0.01]	0.03 [0.00; 0.11]	0.0001 58.1%*
Generalized skin reaction	2	229289	0.35 [0.00; 35.67]	0.09 [0.08; 0.10]	1.69 [0.00; 6.52]	0.0029 58.2%	-					
Needling malpractice	7	1029871	0.22 [0.01; 0.67]	0.00 [0.00; 0.00]	1.04 [0.81; 1.30]	0.0009 99.7%**	7	164146	0.12 [0.02; 0.28]	0.01 [0.00; 0.02]	0.62 [0.28; 1.10]	0.0002 95.1%**
Emotional interference	6	930429	0.20 [0.00; 0.81]	0.02 [0.02; 0.02]	1.24 [0.99; 1.53]	0.0002 98.7%**	7	155131	0.08 [0.00; 0.27]	0.01 [0.00; 0.02]	0.67 [0.51; 0.84]	0.0004 96.8%**
Sleeping problems	5	432529	0.16 [0.00; 0.91]	0.04 [0.03; 0.05]	20.69 [8.19; 37.03]	0.0001 97.1%**	-					
AE caused by moxibustion	4	428682	0.14 [0.00; 1.16]	0.00 [0.00; 0.00]	0.96 [0.60; 1.42]	0.0002 98.3%**	4	145750	0.02 [0.00; 0.18]	0.00 [0.00; 0.01]	0.17 [0.11; 0.25]	0.0001 95.0%**
Respiratory system	3	235637	0.04 [0.00; 0.26]	0.02 [0.01; 0.02]	0.24 [0.00; 0.96]	0.0001 69.0%*	1	3535	0.03 [0.00; 0.11]			

Table 4: Summary risk estimated for different types of adverse events

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses; min: minimum; max: maximum; 95%-CI: 95% confidence interval *: p-value of Q-test for heterogeneity < 0.05; **: p-value of Q-test < 0.00

Discussion

Overall risk for acupuncture related adverse events

To date this is the first systematic review on prospective studies that provides summary risk estimates for acupuncture related adverse events derived from meta-analyses. The obtained results suggest that AE can be expected in every tenth patient that undergoes a series of acupuncture treatments and, overall, in every 13th treatment. Minor AE were common and represented the large majority of reported AE. About half of the reported minor AE are usually mild and transient or might even be regarded as part of the acupuncture treatment or therapeutically intended reactions (bleeding, needle site pain, flare around the needle site).(21) SAE can be expected rarely in about every 10,000th patient in the course of an acupuncture series and, overall, in every 125,000th treatment. Sensitivity analyses excluding studies with zero SAE incidences still suggest SAE being rare (every 7000th patient and every 60,000th treatment) particularly in comparison to SAE risk associated with pharmacological treatments.(16, 53, 54) AE requiring treatment occur uncommonly in about every 900th treatment, but additional AE are likely to also have involved medical decision-making about further diagnostics and follow-up. With meta-analyses for the overall risk of acupuncture related AE covering over 845,637 patients undergoing more than 7.4 million treatments and for the risk of SAE covering more than 1.2 million patients and 10.6 million treatments, the amount of data is equivalent to that on the safety of e.g. common analgesics.(55, 56) This work augments insights on acupuncture related adverse events from previous reviews with either narrow eligibility criteria or focussing on case reports.(17) It includes data from the largest and most rigorous trials on acupuncture safety e.g. from the large nationwide cohort studies conducted in the UK and Germany which had not yet been aggregated.(33, 38-41, 46, 48, 49) Thus, our results provide rigorous support for the previously drawn conclusion (22, 57, 58) that acupuncture is among the safe treatments in medicine with SAE occurring rarely and half of the common minor AE being mild and transient. The uncommon AE requiring treatment necessitate solid medical competence of acupuncturists.

Types of adverse events related to acupuncture and implications for medical education of acupuncturists

Common minor AE were bleeding, needle site pain, other local reactions at the needling site, vegetative reactions, aggravation of symptoms, and AE related to the central nervous system (one to five out of 100 patients). This is in line with other reviews (22, 59) also on auricular (60) and paediatric acupuncture.(58) All other types of minor AE can be regarded as uncommon (1 to 7 out of 1000 patients), despite respiratory reactions that occurred very rarely (4 out of 10,000 patients). SAE most often reported were pneumothorax, strong cardiovascular or vasovagal reactions, and fall or trauma with one to three cases in one million treatments. Several other sometimes fatal SAE repeatedly described in case reports were not observed in the included studies; e.g. traumatic injuries of inner organs, local and systemic infections, subarachnoid bleeding, infective endocarditis, and cardiac tamponade.(61-65) This is likely due to the fact that acupuncturists in most of the studies were well trained, as SAE are claimed to be avoidable by proper acupuncture training and practice. Concordantly, cases of acupuncture malpractice were uncommon in the included trials.

Heterogeneity between studies

Possible causes of the substantial heterogeneity observed in all meta-analyses are differences in patient populations, needling regimens, AE definition, and AE assessment. Sensitivity analyses of trials reporting on adverse reactions with a plausible relationship to acupuncture resulted in only marginally lower overall AE risk estimates, but in a 50% lower SAE risk per patient and a 30% lower SAE risk per treatment. Reporting of SAE irrespective of the relationship to acupuncture is surely more conservative but likely to cause risk overestimation. In line with this, the causality of more than half of the SAE was rated as unlikely or unclassifiable by two independent acupuncture experts.

The variety of combinations of further patient treatment and assessment related factors prevented meaningful subgrouping of studies for additional sensitivity analyses, and the likeliness of their contribution to the observed heterogeneity makes formal assessment for publication bias unadvisable.(66) However, some distinct observations are worth to be discussed. Certain patient populations might be at higher risk to experience acupuncture related AE; e.g. in one study conducted among CMD patients AE were prominently frequent.(37) The role of acupuncture regimens in explaining heterogeneity could not be determined due to the limited information about number, location, and stimulation of needles. In contrast, the number of treatments per acupuncture series and study type seemed not to have impacted reported AE incidences.

A further possible cause of heterogeneity are differences in contrasting AE from therapeutically intended reactions that form part of acupuncture treatment; e.g. in contrast to international consensus, (18) aggravated symptoms were not or only in part counted as AE in two studies. (32, 48) Local reactions such as bleeding, pain, and flare at the needling site, that represented half of the AE reported, are referred to as beneficial signs in standard acupuncture textbooks and by authors themselves.(20, 33) As the principle of acupuncture is to induce endogenous anti-nociceptive mechanisms and anti-inflammatory humoral responses through micro-trauma of the skin and tissue, it can be argued that moderate local reactions are indeed desired reactions indicating an induction of regulative processes. Mild pain and a flare at the needling site have been linked to important neurophysiological mechanisms of acupuncture.(21) Additionally, aching or soreness at the needling site might be part of the intended deqi sensation (propagated sensation along the channels) supposedly related to acupuncture effectiveness.(19) The loss of small drops of blood upon needle withdrawal is interpreted as a sign for the patient's constitution called "excess" or "excess heat" in TCM terminology and was suggested not to be interpreted as AE.(67) On the other hand, standard text books explicitly explain needling techniques avoiding pain and bleeding.(20, 68) This debate calls for a uniform internationally recognized consensus on the definition of local acupuncture reactions as AE e.g. according to their quality and intensity.

In addition, included studies differed in reporters (acupuncturists, patients, acupuncturists also questioning patients, and independent assessors), the type of documentation (selection list, open questions, or a combination of both), and assessment time points. Due to the large variability of combinations the individual impact of these factors could not be estimated, but literature suggests that patients report more AE than therapists,(69) and that open questions presented to patients lead to lower risk estimates than the presentation of a selection list of possible AE.(31) Thus, standardized AE assessment methods should be established for acupuncture studies.

Risk of bias in included studies

Although, large prospective studies are among the most important sources of safety data, they come with the known risk for information, selection, and confounding bias.(70) Risk of information bias was mostly related to poor reporting of acupuncture regimens and the discrepancies in AE definition and assessment. This is in line with the shortcoming identified for reporting of AE in acupuncture randomized controlled trials.(71) Possible causes of selection bias identified were mainly voluntary participation of practitioners, unsystematic patient selection, and study conductance in highly specialized institutions. Practical reasons make these causes of selection bias inherent to safety studies. They, however, are unlikely to importantly impair external validity, considering the large number of patients and treatments, the variety of countries in which studies were conducted, and the inclusion of different study designs. Future large scale comparative safety studies along with modern statistical methods for confounder adjustment could be used to contrast AE risks related acupuncture to AE risks associated with other treatments and to identify patient and treatment characteristics associated with AE in real world clinical settings.(72)

Limitations

First, it is debatable whether studies should be summarized irrespective of whether AE not necessarily related to acupuncture or adverse reactions likely caused by acupuncture were reported. In order to provide the most comprehensive information possible respective sensitivity analyses were conducted. Another limitation with regard to the inclusion criteria is the restriction to articles published in German or English as many studies on acupuncture are published in Chinese. Additionally, the risk estimates for the different types of minor adverse events are likely to be slightly overestimated and should be interpreted as a rough indication that allows to distinguish frequent from less frequent acupuncture related minor AE. In categorizing the minor AE it was disregarded that several different AE falling in one category could have occurred in the same patient or during the same treatment. Also, calculations of risks in treatments with AE per total number of treatments could not adjust for the fact that multiple AE assessments in the same patient are not independent. Furthermore, zero incidences of certain types of AE were not available. Finally, the causality assessment presented for SAE is limited to expert opinions and is only based on the information provided in the respective article. Such an evaluation does not replace a rigorous causality assessment that would involve querying patients and therapists.

Clinical implications

Patients should be informed that acupuncture commonly causes minor AE, but rarely SAE. Examples for SAE should at least cover the most frequent ones, pneumothorax and strong cardiovascular or vasovagal reactions potentially leading to fall or trauma, along with the respective incidence of 1-3 per million treatments. Patients should also be made aware of the fact that great part of the minor AE are either very mild or even intended effects that indicate a beneficial physiological reactions. However, they should be encouraged to report any prolonged discomfort or pain that are to be avoided during treatment. Acupuncturists should carefully balance treatment intensity according to patients' reactions in order to minimize AE. They should assess local AE upon needle withdrawal and query patients about AE directly after treatment as well as at the subsequent visit. Therapists should be aware that, although uncommon, AE requiring treatment can be expected and necessitate medical decision making. Medical competence is also required for the indication of acupuncture in patients at high risk for AE or those in which AE could lead to particular aversive outcomes, such as pregnant women, elderly and patients with cardiovascular comorbidities. In these patients acupuncture can be especially beneficial, as conventional treatments e.g. with analgesics are often limited by side effects or drug interactions, but selection of acupuncture regimens needs to involve careful risk-benefit considerations. Theses medical competences required to provide optimal patient safety should also be reflected by acupuncture education standards and regulations. At this policy makers should take into account the worldwide popularity of acupuncture which is likely to further increase as its scientific level of evidence has led to more than 4000 practice guidelines recommending acupuncture for different mostly pain indications.(69)

Conclusion

Acupuncture can be considered among the safer treatments in medicine. It rarely causes SAE and the majority of the common minor AE are very mild. AE requiring medical management are uncommon. For optimal patient safety acupuncture education standards regulations should reflect that solid medical competence of acupuncturists is required to manage AE properly and to minimize the risk of malpractice. Clinical and methodological heterogeneity calls for an international consensus on AE assessment tools in acupuncture studies and criteria for differentiating acupuncture related AE from therapeutically desired reactions as well as identification of patient related risk factors for acupuncture related AE. In particular, comparative safety studies are needed to contrast acupuncture to standard care in its main indications.

Figure legends

Figure 1: Flow diagram

Designed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)(24)

Figure 2: Risk of bias assessment

Risk of bias assessment was conducted according to Faillie et al.(29) L – green: low risk of bias, U – yellow: unclear risk of bias, H – red: high risk of bias

Figure 3: Meta-analyses of the overall risk for acupuncture related adverse events

Summary risk estimates for adverse events (AE) were calculated as the number of patients or treatments with at least one AE relative to the total number of patients or treatments, respectively. Data on AE reports of patients (pat.) and therapists (ther.) from the article published by Weidenhammer et al. in 2008 were handled separately.

Figure 4: Meta-analyses of the overall risk for serious adverse events related to acupuncture

Summary risk estimates for serious adverse events (SAE) were calculated as the number SAE cases relative to the total number of patients or treatments, respectively. Data from the article published by Weidenhammer et al. in 2008 refer to the AE reports of the therapists (ther.).

Figure 5: Meta-analyses of the overall risk for adverse events (AE) requiring treatment

Summary risk estimates for AE requiring treatment were calculated as the number of patients with such AE relative to the total number of patients.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. DI reports to recieve honorarium and travel costs from non-profit academic organizations, physician chambers and universities for teaching and lecturing and to serve as president of the German Medical Acupuncture Association (Deutsche Ärztegesellschaft für Akupunktur, DÄGfA, a non-profit medical associations). PB declares to recieve honorarium and travel costs from non-profit academic organizations and universities for teaching and lecturing and to be member of the scientific advisory board of the DÄGfA. WZ and TS declare: no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

DI, PB and WZ defined the research question as well as in and exclusion criteria for this systematic review. WZ, TS and PB were responsible for article screening, data extraction and classifications of adverse events. TS and PB performed the quality assessment. Questions and discrepancies were discussed among all authors until consent was achieved. PB conducted the meta-analyses and designed table and figures. All authors contributed to drafting the manuscript and approved its final version for publication.

The corresponding author (PB) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. As the senior author, DI is the guarantor of the work presented in this manuscript. DI accepts full responsibility for the finished article, has access to any data and controlled the decision to publish

Transparency declaration

The lead author DI affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that the review and analyses were conducted as planned.

Ethical approval

As our work represents an analysis of already published data, approval by an ethics committee was not required.

Data sharing

The full set of extracted data and the R-code underlying the meta-analyses are available from the corresponding and senior author (Petra.Baeumler@med.uni-muenchen.de, Dominik.Irnich@med.uni-muenchen.de).

Dissemination to participants and related patient and public communities

Authors plan to disseminate the findings of this review to patients, clinicians, policy makers and the general public through various channels including newsletters, newspapers and magazines. In special regard to patient information, results will be shared during patient seminars and information events, and a concise version of the results will be made available for non-profit acupuncture organisations to be presented on their webpages.

Trial registration

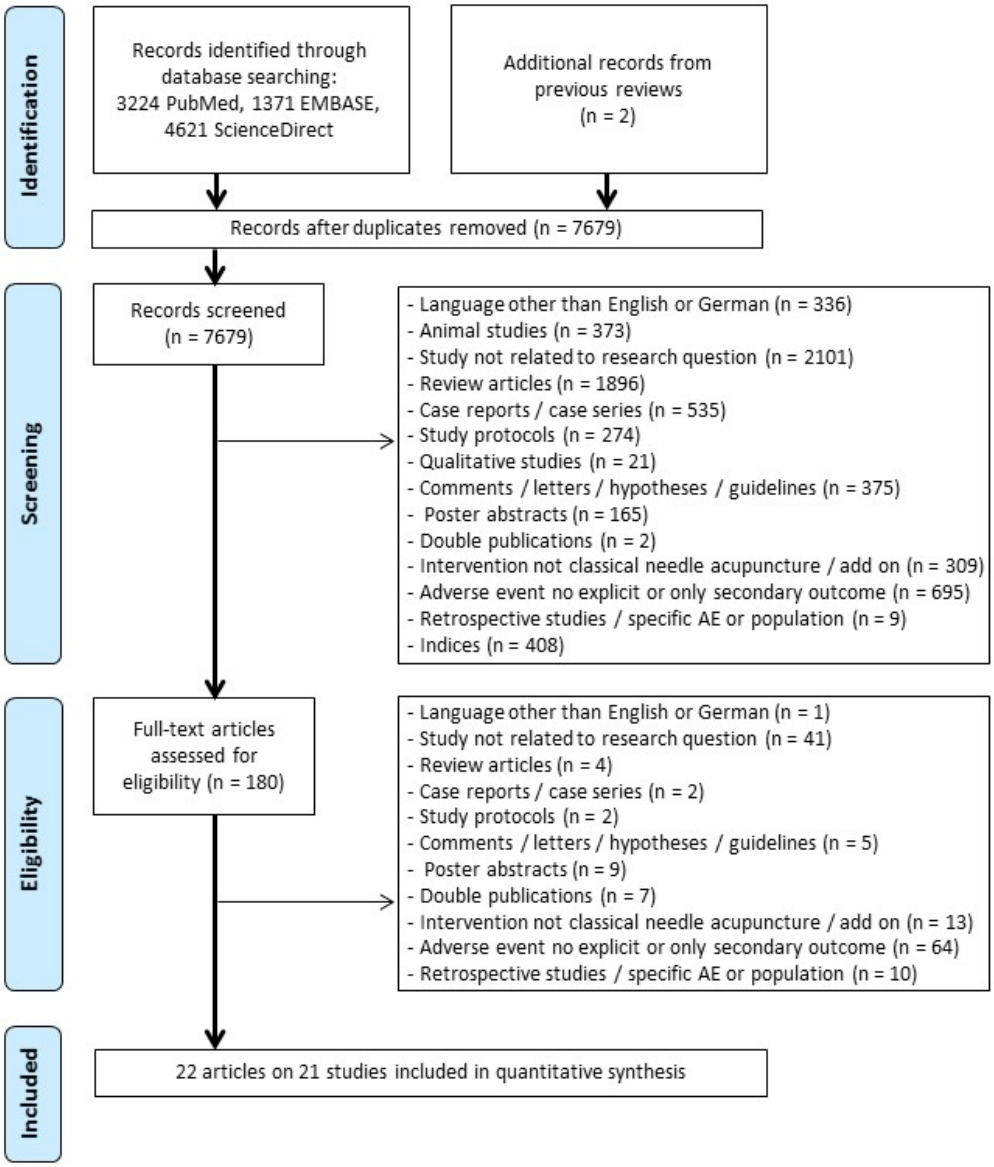
PROSPERO registration number CRD42020151930. To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. It has not been checked for eligibility or for sense by the PROSPERO team.

References

1. Ammon K, Cardini F, Daig U, Dragan S, Frei-Erb M, Hegyi G, et al. Final Report of CAMbrella Work Package 5 - Helath Technology Assessment (HTA) and a map of CAM provision in the EU. CAMbrella - A pan-European research network for Complementary and Alternative Medicine (CAM); 2013 [updated 17.09.2013]. 14]. Available from: https://phaidra.univie.ac.at/view/o:300096.
2. British Acupuncture Council. Acupuncture practitioners in the UK 2016 [updated 2016]. Available from: https://www.acupuncture.org.uk/public-content/about-the-bacc/4115-acupuncture-practitioners-in-the-uk.html.
3. Cui J, Wang S, Ren J, Zhang J, Jing J. Use of acupuncture in the USA: changes over a decade (2002-2012). Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2017;35(3):200-7.
4. Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. J Pain. 2018;19(5):455-74.
5. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev. 2016(6):Cd001218.
6. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Shin BC, et al. Acupuncture for the prevention of tension-type headache. Cochrane Database Syst Rev. 2016;4:Cd007587.
7. Tedesco D, Gori D, Desai KR, Asch S, Carroll IR, Curtin C, et al. Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty: A Systematic Review and Meta-analysis. JAMA surgery. 2017;152(10):e172872.
8. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British journal of anaesthesia. 2008;101(2):151-60.
9. Lee A, Chan SK, Fan LT. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2015(11):Cd003281.
10. Feng S, Han M, Fan Y, Yang G, Liao Z, Liao W, et al. Acupuncture for the treatment of allergic rhinitis: a systematic review and meta-analysis. American journal of rhinology & allergy. 2015;29(1):57-62.
11. Yang A, Wu HM, Tang JL, Xu L, Yang M, Liu GJ. Acupuncture for stroke rehabilitation. Cochrane Database Syst Rev. 2016(8):Cd004131.
12. Smith CA, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. Cochrane Database Syst Rev. 2018;3:Cd004046.
13. Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA. 2018;320(2):167-76.
14. Brinkhaus B, Roll S, Jena S, Icke K, Adam D, Binting S, et al. Acupuncture in Patients with Allergic Asthma: A Randomized Pragmatic Trial. J Altern Complem Med. 2017;23(4):268-77.
15. Whiskey E, Taylor D. A review of the adverse effects and safety of noradrenergic antidepressants. Journal of psychopharmacology (Oxford, England). 2013;27(8):732-9.
16. Carter GT, Duong V, Ho S, Ngo KC, Greer CL, Weeks DL. Side effects of commonly prescribed analgesic medications. Physical medicine and rehabilitation clinics of North America. 2014;25(2):457-70.
17. Chan MWC, Wu XY, Wu JCY, Wong SYS, Chung VCH. Safety of Acupuncture: Overview of Systematic Reviews. Sci Rep. 2017;7(1):3369.
18. White A, Boon H, Alraek T, Lewith G, Liu JP, Norheim AJ, et al. Reducing the risk of complementary and alternative medicine (CAM):Challenges and priorities. Eur J Integr Med. 2014;6(4):404-8.
19. Ren YL, Guo TP, Du HB, Zheng HB, Ma TT, Fang L, et al. A survey of the practice and perspectives of chinese acupuncturists on deqi. Evidence-based complementary and alternative medicine : eCAM. 2015;2015:684708.
20. Shanghai College of Traditional Medicine. Acupuncture - a comprehensive text. Seattle, USA: Eastland Press; 1981.
21. Zhu H. Acupoints Initiate the Healing Process. Medical acupuncture. 2014;26(5):264-70.
22. Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. Am J Med. 2001;110(6):481-5.
23. University of York Y, UK. International prospective register of systematic reviews (PROSPERO). Available from: https://www.crd.york.ac.uk/prospero.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.

25. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000;283(15):2008-12.
26. European Medicines Agency. Guideline for good clinical practice E6(R2). 2016. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.
27. the UPPSLA MONITORING CENTRE. WHO-UMC system for standardised case causality assessment. 2013. Available from: https://www.who.int/publications/m/item/WHO-causality-assessment.
28. Council for International organizations of medical sciences - CIOMS. Guidelines for Preparing Core Clinical-Safety Information on Drugs Second Edition – Report of CIOMS Working Groups III and V. 1999. Available from: https://cioms.ch/shop/product/guidelines-preparing-core-clinical-safety-information-drugs-second-edition-report-cioms-working-groups-iii-v/.
29. Faillie JL, Ferrer P, Gouverneur A, Driot D, Berkemeyer S, Vidal X, et al. A new risk of bias checklist applicable to randomized trials, observational studies, and systematic reviews was developed and validated to be used for systematic reviews focusing on drug adverse events. J Clin Epidemiol. 2017;86:168-75.
30. Schwarzer G. meta: {A}n {R} package for meta-analysis. R News. 2007;7(3):40-5.
31. Chung KF, Yeung WF, Yu YM, Kwok CW, Zhang SP, Zhang ZJ. Adverse Events Related to Acupuncture: Development and Testing of a Rating Scale. Clin J Pain. 2015;31(10):922-8.
32. da Silva JBG, Saidah R, Megid CBC, Ramos NA. Adverse events following acupuncture: A prospective survey of 13,884 consultations in a university out-patient acupuncture training clinic in Brazil. Eur J Integr Med. 2014;6(4):488-91.
33. Endres HG, Molsberger A, Lungenhausen M, Trampisch HJ. An internal standard for verifying the accuracy of serious adverse event reporting: the example of an acupuncture study of 190,924 patients. Eur J Med Res. 2004;9(12):545-51.
34. Ernst G, Strzyz H, Hagmeister H. Incidence of adverse effects during acupuncture therapy—a multicentre survey. Complementary therapies in medicine. 2003;11(2):93-7.
35. Furuse N, Shinbara H, Uehara A, Sugawara M, Yamazaki T, Hosaka M, et al. A Multicenter Prospective Survey of Adverse Events Associated with Acupuncture and Moxibustion in Japan. Medical acupuncture. 2017;29(3):155-62.
36. Leung PC, Zhang L, Cheng KF. Acupuncture: Complications are preventable not adverse events. Chin J Integr Med. 2009;15(3):229-32.
37. List T, Helkimo M. Adverse events of acupuncture and occlusal splint therapy in the treatment of craniomandibular disorders. CRANIO. 1992;10(4):318-26.
38. MacPherson H, Scullion A, Thomas KJ, Walters S. Patient reports of adverse events associated with acupuncture treatment: A prospective national survey. Qual Saf Health Care. 2004;13(5):349-55.
39. MacPherson H, Thomas K. Short term reactions to acupuncture--a cross-sectional survey of patient reports. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2005;23(3):112-20.
40. MacPherson H, Thomas K, Walters S, Fitter M. A prospective of adverse events and treatment reactions following 34,000 consultations with professional acupuncturist. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2001;19(2):93-102.
41. Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, et al. Prospective Investigation of Adverse Effects of Acupuncture in 97 733 Patients. Arch Intern Med. 2004;164(1):104-5.
42. Melchart DV, Hager S, Weidenhammer W, Liao JZ, Liu Y, Linde K. Adverse effects and concomitant symptoms associated with acupuncture treatment - A pilot study. Akupunktur. 1998;26(2):87-92.
43. Odsberg A, Schill U, Haker E. Acupuncture treatment: side effects and complications reported by Swedish physiotherapists. Complementary therapies in medicine. 2001;9(1):17-20.
44. Park JE, Lee MS, Choi JY, Kim BY, Choi SM. Adverse events associated with acupuncture: A prospective survey. J Altern Complem Med. 2010;16(9):959-63.
45. Park SU, Ko CN, Bae HS, Jung WS, Moon SK, Cho KH, et al. Short-term reactions to acupuncture treatment and adverse events following acupuncture: A cross-sectional survey of patient reports in Korea. J Altern Complem Med. 2009;15(12):1275-83.
46. Weidenhammer W, Streng A, Melchart D, Linde K. Unerwünschte Wirkungen und Komplikationen bei Akupunkturbehandlung: Ergebnisse der großen Beobachtungsstudie im Rahmen des Modellvorhabens der Ersatzkassen. Dtsch Zeitschrift für Akupunkt. 2008;51(3):6-14.
47. Wen Y, Zhang C, Zhao XF, Deng SZ, He S, Huang LH, et al. Safety of different acupuncture manipulations for posterior circulation ischemia with vertigo. Neural Regen Res. 2016;11(8):1267-73.

48. White A, Hayhoe S, Hart A, Ernst E. Survey of adverse events following acupuncture (SAFA): A prospective study of 32,000 consultations. Acupuncture in medicine : journal of the British Medical Acupuncture Society. 2001;19(2):84-92.
49. Witt CM, Pach D, Brinkhaus B, Wruck K, Tag B, Mank S, et al. Safety of acupuncture: Results of a prospective observational study with 229,230 patients and introduction of a medical information and consent form. Forsch Komplementmed. 2009;16(2):91-7.
50. Yamashita H, Tsukayama H, Hori N, Kimura T, Tanno Y. Incidence of adverse reactions associated with acupuncture. J Altern Complem Med. 2000;6(4):345-50.
51. Yamashita H, Tsukayama H, Tanno Y, Nishijo K. Adverse events in acupuncture and moxibustion treatment: A six-year survey at a national Clinic in Japan. J Altern Complem Med. 1999;5(3):229-36.
52. Zhao L, Zhang FW, Li Y, Wu X, Zheng H, Cheng LH, et al. Adverse events associated with acupuncture: Three multicentre randomized controlled trials of 1968 cases in China. Trials. 2011;12:no pagination.
53. Degner D, Grohmann R, Kropp S, Ruther E, Bender S, Engel RR, et al. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry. 2004;37 Suppl 1:S39-45.
54. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. American journal of therapeutics. 2000;7(2):115-21.
55. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. Bmj. 2011;342:c7086.
56. Martin Arias LH, Martin Gonzalez A, Sanz Fadrique R, Salgueiro Vazquez E. Gastrointestinal safety of coxibs: systematic review and meta-analysis of observational studies on selective inhibitors of cyclo-oxygenase 2. Fundamental & clinical pharmacology. 2018.
57. Wang C, Tan B, Williams A. Safety and side effects of acupuncture therapy in Australia: A systematic review. Eur J Integr Med. 2019.
58. Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. Pediatrics. 2011;128(6):e1575-87.
59. Wang CC, Tan JY, Williams A. Safety and side effects of acupuncture therapy in Australia: A systematic review. Eur J Integr Med. 2019;27:81-9.
60. Tan JY, Molassiotis A, Wang T, Suen LK. Adverse events of auricular therapy: a systematic review. Evid Based Complement Alternat Med. 2014;2014:506758.
61. Zhang J, Shang H, Gao X, Ernst E. Acupuncture-related adverse events: a systematic review of the Chinese literature. Bull World Health Organ. 2010;88(12):915-21C.
62. Xu S, Wang L, Cooper E, Zhang M, Manheimer E, Berman B, et al. Adverse events of acupuncture: a systematic review of case reports. Evid Based Complement Alternat Med. 2013;2013:581203.
63. He W, Zhao X, Li Y, Xi Q, Guo Y. Adverse events following acupuncture: a systematic review of the Chinese literature for the years 1956-2010. J Altern Complem Med. 2012;18(10):892-901.
64. Ernst E, Lee MS, Choi TY. Acupuncture: does it alleviate pain and are there serious risks? A review of reviews. Pain. 2011;152(4):755-64.
65. Ullah W, Ahmad A, Mukhtar M, Virk HUH, Sarwar U, Figueredo V. Acupuncture-Related Cardiac Complications: A Systematic Review. J Invasive Cardiol. 2019;31(4):E69-E72.
66. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ. 2006;333(7568):597-600.
67. Zhu HZ. Running a Safe and Successful Acupuncture Clinic. Edinburgh, London, New York, Oxford, Philadelphia, St Louis, Sydney, Toronto: Elsevier - Churchill Livingstone; 2006.
68. Deng L, Gan Y, He S, Ji X, Y. L, Wang R, et al. Chinese Acupuncture and Moxibustion. 2nd ed. Beijing, China: Foreign Languages Press; 1999.
69. Schwaneberg T, Witt CM, Roll S, Pach D. Comparing physicians' and patients' reporting on adverse reactions in randomized trials on acupuncture-a secondary data analysis. BMC Complement Altern Med. 2019;19(1):223.
70. Suissa S. Statistical methods in pharmacoepidemiology: advances and challenges. Stat Methods Med Res. 2009;18(1):3-6.
71. Capili B, Anastasi JK, Geiger JN. Adverse event reporting in acupuncture clinical trials focusing on pain. Clin J Pain. 2010;26(1):43-8.
72. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. Bmj. 2019;367:l5657.



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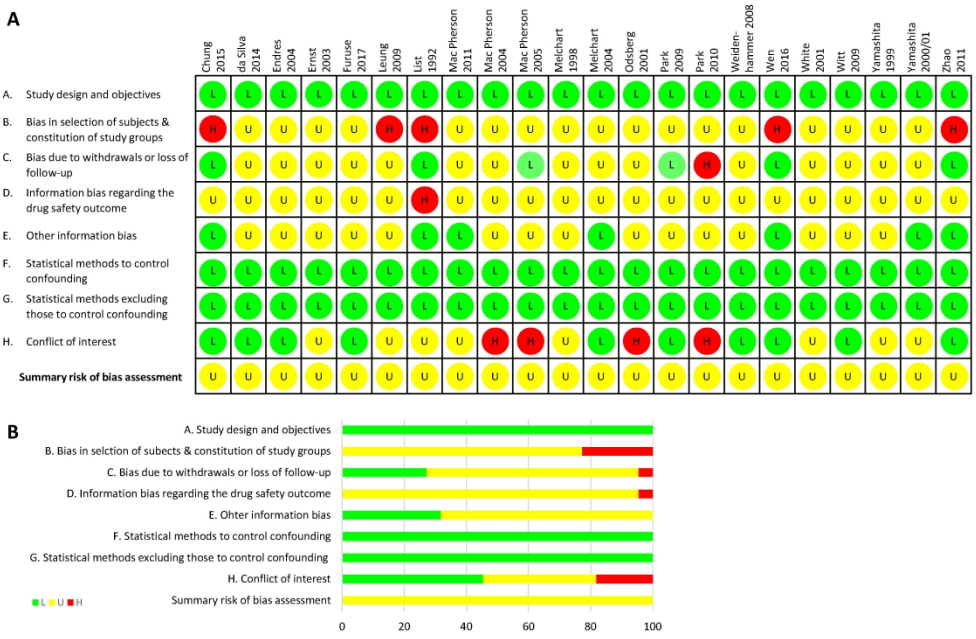

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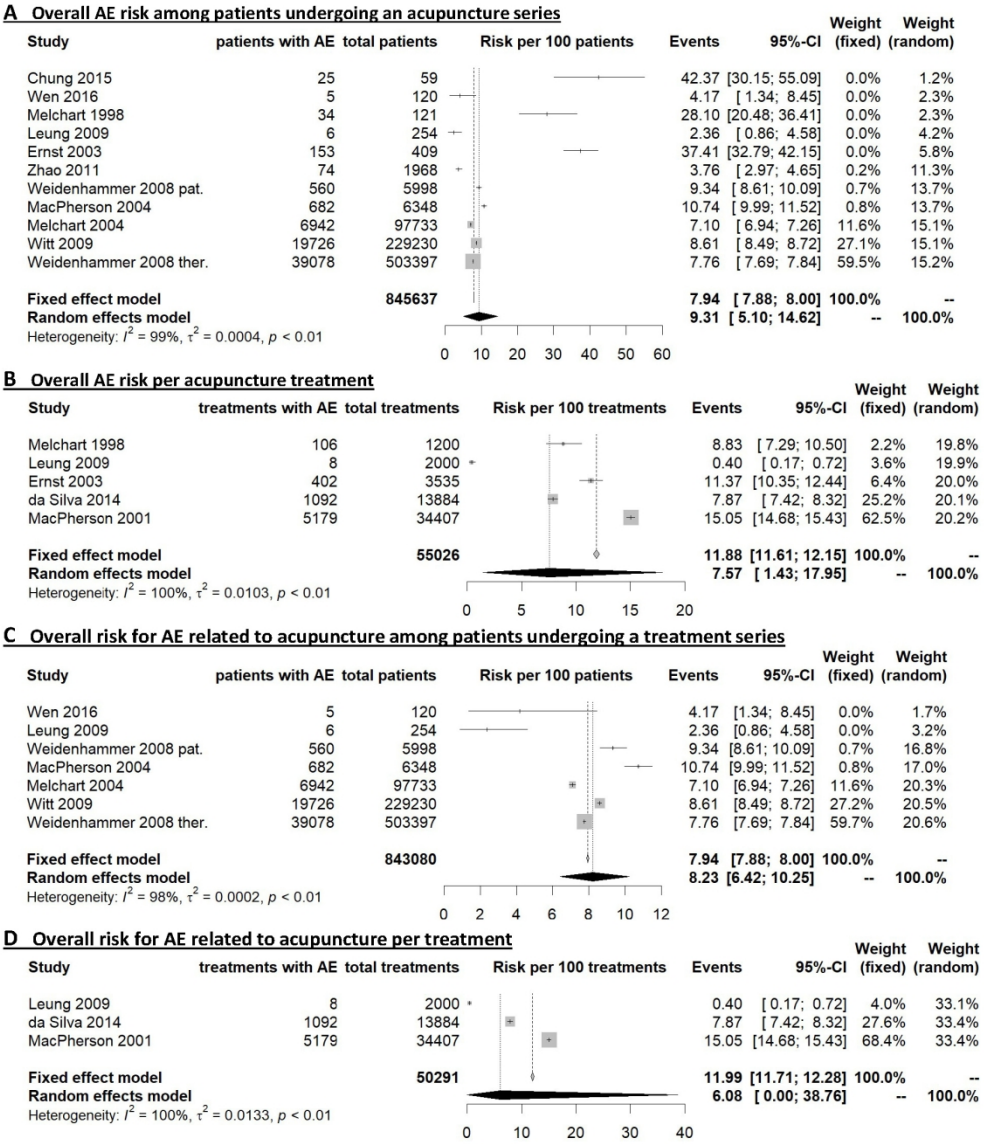

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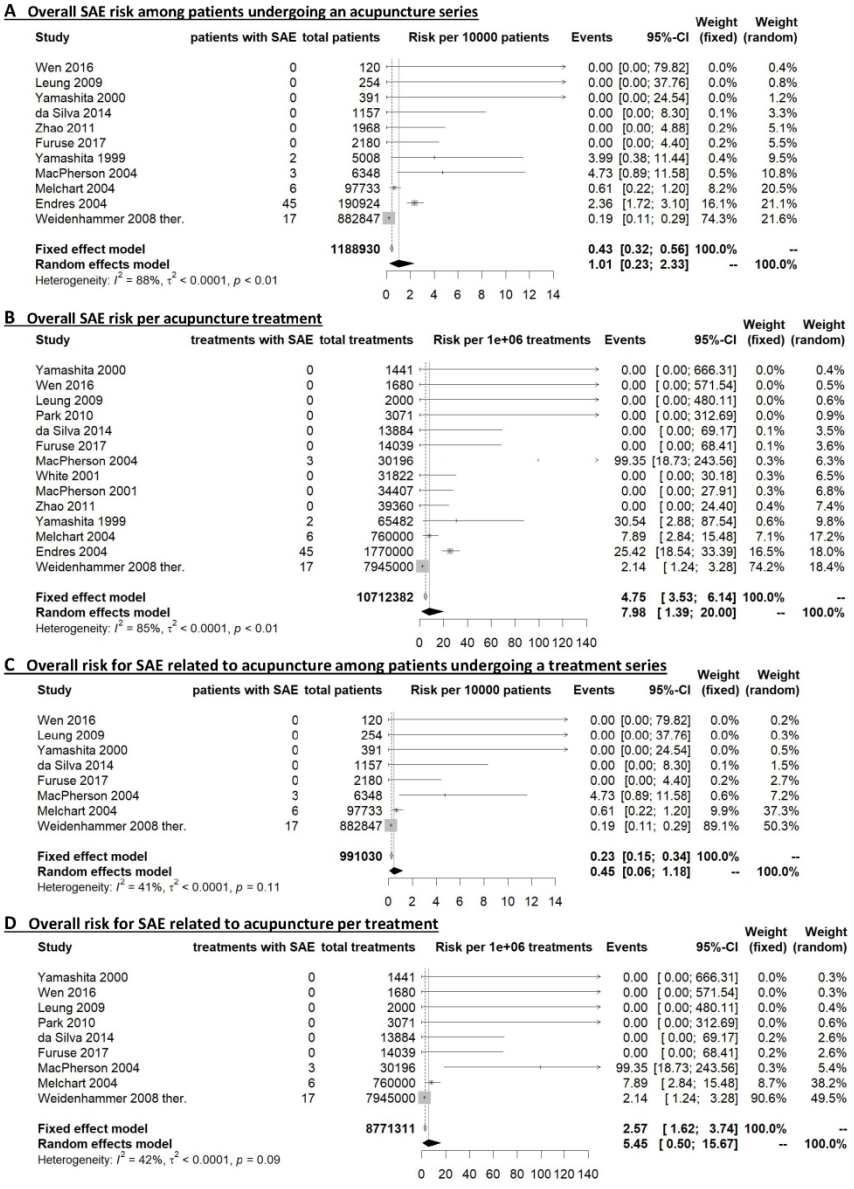

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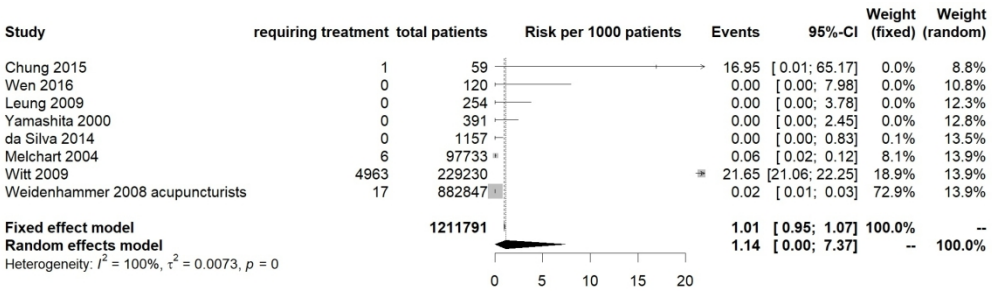


286x82mm (180 x 180 DPI)

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Acupuncture related adverse events - a systematic review of prospective clinical trials

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

English

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.
19/09/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.
31/12/2019

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Piloting of the study selection process

Piloting of the study selection process

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Dr. Petra Bäumler

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Petra

7. * Named contact email.

Give the electronic email address of the named contact.

Petra.Baeumler@med.uni-muenchen.de

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Dr. Petra Bäumler

Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich

Pettenkoferstr. 8a

80336 Munich, Germany

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

0049-89-4400-53625

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Petra Baeumler. Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich
Professor Dominik Irnich. Multidisciplinary Pain Center, Department of Anaesthesiology, University Hospital LMU Munich
Mrs Theresa Stübinger. Multidisciplinary Pain Center, Department of Anaesthesiology, Universtiy Hospital LMU Munich

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

No funding is received

State the funder, grant or award number and the date of award
Grant number(s)

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

Yes

Petra Bäumler and Dominik Irnich receive honoraria and travel costs from non-profit academic organizations, physician chamber and universities for teaching and lecturing. Theresa Stübinger declares no conflict of interest

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Wenyue Zhang. School of Acupuncture, Moxibustion and Tuina, Beijing University of Chinese Medicine

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the risk for minor and serious adverse events caused by acupuncture?

What kind of adverse events can be caused by acupuncture?

What is the risk of the different types of acupuncture related adverse events?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Databases: PubMed, Scopus, EMBASE

Publication period: inception to 15th September 2019

Search Terms: acupuncture, adverse event(s), adverse effect(s)

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Acupuncture is the insertion of fine needles at certain points, so called acupuncture points, on the patients body for therapeutic or preventive purposes. Acupuncture originates from ancient Chinese medicine, but is nowadays used worldwide in many different variations. There is level 1 for its effectiveness in acute and chronic pain. Needles are stimulated manually, electrically. Often moxibustion is used as an adjunct. The safety of acupuncture has been debated, and surely needle penetration can cause harms, such as tissue damage, peripheral nerve injury and bleeding. In comparsion to analgesic drugs for example, risk and consequences of adverse events are deemed minor, but reviews on the safety of acupuncture are either outdated or lack an assessment of study quality.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Humans treated by needle acupuncture

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Acupuncture involving either manual or electrical needle stimulation with or without moxibustion

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

As the aim of this review is to estimate the crude risk of acupuncture related adverse events, comparator group data are not relevant.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Inclusion criteria:

Prospective study

Primary outcome is the risk of acupuncture related adverse events

Treatment involves acupuncture with needles that are stimulated manually or electrically either in combination with or without moxibustion

Articles published in English or German before 15th of September 2019

Exclusion criteria

Treatment involves injection

Treatment involves skin penetration with any other device than classcial acupuncture needles such as press needles, cauterization devices etc.

Treatment is restricted to non-penetrating stimulation such as laser acupuncture, acupressure, transcutaneous electrical nerve stimulation or moxibustion

Treatment is restricted to particular body parts associated with low risk of adverse events such as auricular or one-point acupuncture

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Risk of serious and minor acupuncture related adverse events (AE) as number of AE per treatment and patients with AE per 100.000 patients treated

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

adverse events ocurring during or after acupuncture treatment

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Type of adverse events caused by acupuncture

Risk of the different types of acupuncture related adverse-events

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

adverse Events ocurring during or after acupuncture treatment

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Incidence of acupuncture related adverse events will be extracted as the number of adverse events per treatment and as number of patients experiencing these adverse events per the total number of patients treated. Data extraction will be performed by two independent reviewers who will extract all available data on acupuncture related adverse events from identified studies. This includes extraction of the total number of and/or patients with minor and serious adverse events as well as extraction of the numbers of and/ or patients with all types of adverse events separately in relation to the number of treatments and/or total number of patients treated. The different types of adverse events will be categorized into supersets of adverse events whose risk is calculated separately.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Included studies will be assessed for risk of bias according to a checklist developed by Faillie and colleagues for systematic reviews focusing on adverse events.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

We will provide the reader with the range (min and max) and the median of the total risk to suffer from an minor and serious adverse event during or after acupuncture treatment that was identified by the studies. The same measures will be provided for the risks of the supersets of adverse events identified from the different studies.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

It is likely that certain subsets of patients are at a higher risk for acupuncture related adverse events. According to the obtained results we will provide characteristics and separate summaries of studies including patients with a high and low risk profile.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews

No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
Yes

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.
Germany

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

The review has not been registered elsewhere.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

A paper presenting the review results will be submitted to a journal listed in MEDLINE. Furtermore, results will be published at international congresses.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

acupuncture, adverse-event, adverse-effect, safety, needling, moxibustion, traditional Chinese mecicine

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint. List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2 / 4 / 19
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 / 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 / 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 - 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 Figure 2A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3 - 5 Table 2 / 4 Suppl. S6 / S7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9 - 12 Figure 3 - 5 Table 4 Suppl. S6 / S7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 Figure 5 B
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 - 12 Figures 3C/D 4C/D
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	page5 table 1
4	Type of exposure or intervention used	page5 table 1
5	Type of study designs used	page5 table 1
6	Study population	page5 table 1
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	title page
8	Search strategy, including time period included in the synthesis and key words	page 5
9	Effort to include all available studies, including contact with authors	page 5
10	Databases and registries searched	page 5
11	Search software used, name and version, including special features used (eg, explosion)	none
12	Use of hand searching (eg, reference lists of obtained articles)	page 5
13	List of citations located and those excluded, including justification	table1 figure 1
14	Method of addressing articles published in languages other than English	page 5
15	Method of handling abstracts and unpublished studies	figure 1
16	Description of any contact with authors	none
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	pages 4, 5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	page 5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	page 5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	n.a.
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	page 6
22	Assessment of heterogeneity	page 6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	page 6
24	Provision of appropriate tables and graphics	Tables 1-4, figures 1-5 Suppl. S1-7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	figs 3-5
26	Table giving descriptive information for each study included	page 7 table 1
27	Results of sensitivity testing (eg, subgroup analysis)	pages 10-12 figures 3-5
28	Indication of statistical uncertainty of findings	pages 10-12 figures 3-4

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	pages 14-15 Suppl. S4
30	Justification for exclusion (eg, exclusion of non-English language citations)	page 16
31	Assessment of quality of included studies	page 15
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Pages 14-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	page 16
34	Guidelines for future research	pages 15 - 16
35	Disclosure of funding source	page 18

Bleeding		
• Bleeding • Bleeding at needling site • Mild / transient / minor bleeding • Subcutaneous bleeding • Hematoma • Minor hematoma • Subcutaneous / superficial hematoma	• Small hemorrhage • Lesion of blood vessel • Bruising • Bruising at needling site • Mild / transient bruising • Heavy bruising • Subcutaneous bruise	• Ecchymosis or hematoma accompanied by pain • Ecchymosis or hematoma without pain • Petechia or ecchymosis
Local pain		
• Pain • Needle (-site) pain • Pain where needle was inserted / at the site of the needle / in the punctured region • Mild / transient pain at needling site • Severe / strong / significant pain at needling site	• Pain upon insertion / stimulation • Pain while needle was in place • Pain upon needle withdrawal at the acupuncture point • Pain after needle was removed • Remaining / residual needle site pain • Prolonged / unacceptable pain at needle site	• Mild pain at the acupuncture site more than one hour after treatment • Pain disappearing after > 3 days • Chest pain (pneumothorax ruled out) • Electroacupuncture problems e.g. too strong current resulting in pain • Local muscle pain • Unknown pain
Other local AE		
• Wheal • (Local) swelling • Redness • Flare • Localized erythema • Needle-site / local skin reaction • (Skin) irritation at acupuncture point • Skin infection • Local (skin) infection	• Inflammation at application site • Itch • Itching and redness • Itching in the punctured region • Itching and erythema (suspected contact dermatitis) • Local allergic reaction (uticaria) • Needle allergy • Allergic phenomena / reaction	• Significant rash on abdomen few days after acupuncture • Cellulitis after treatment of edematous leg • Edema in m. tibialis with anterior toe lifting weakness (fully resolved) • Other local AE (around the acupuncture site)
Central nervous system		
• Aphasia • Dizziness • Mild / transient dizziness • Imbalance • Severe dizziness, vertigo or loss of balance	• Vertigo • Disorientation (length unspecified, 1 h, 1 day) • Severe disorientation • Disturbed speech • Slurred speech	• Disturbed vision • Spontaneous sensory perceptions • Shivering • Seizure shortly after treatment • Tremor
Peripheral nervous system		
• Cold sensation at needling site • Feeling of acupuncture point at contralateral arm • Paraesthesia • Temporary paraesthesia • Tingling • Tingling, prickling, burning, dysesthesia	• Prolonged deqi • Strong acupuncture or heavy sensation • Hypaesthesia • Numbness • Numbness in upper extremity • Numbness and unusual sensation • Severe stiffness or numbness	• Hypaesthesia with numbness for three days • Insensibility • Itching, pins & needles, tingling or burning sensation • Nerve irritation • Neuritis
Aggravation of symptoms		
• Aggravation • Aggravation of complaints / existing ailment / existing symptoms • Unexpected, severe or prolonged worsening of symptoms • Aggravation of symptoms during acupuncture session / after treatment	• Transient aggravation of symptoms • Aggravation of existing symptoms followed by improvement • Deterioration / exacerbation of symptoms • General aggravation of symptoms • Worsening of health state	• Worsening of condition (after removing needles) • Headache and or facial pain • pressure and or tension in the teeth • Increased pain
Vegetative nervous system		
• (Generalized) sweating • Isolated sweating of hands • Mild sweating • Flushed cheeks and body warmth • Hot flash • Feeling of warm / heat / cold • Coldness / feeling cold • Freezing • (Feeling of) fatigue • Extreme feeling of fatigue • Feeling tired (mild transient) • Tiredness and exhaustion	• Abnormal tiredness • Severe / significant tiredness or exhaustion • Lethargy • Dazed • Vasovagal reaction: collapse, dizziness, nausea & vomiting • Unconsciousness • Fainting • Faint / dizzy • Feel faint / drowsy • Feel faint (significant)	• Significant / severe drowsiness • Drowsiness not causing hazard • Prolonged drowsiness (one day, one week) • Drowsiness or restlessness • Orthostatic problems • Malaise • Poor concentration • Dry lips / mouth • Xerostomia • Hunger / thirst

Motor system		
• Cramp	• Heavy legs	• Joint problems
• General muscle tenderness	• Knee went weak	• Restricted movement
• Muscle spasm / tension / weakness	• Weakness in legs / legs or arms	• Stiffness
Distant pain		
• Pain / ache / discomfort other than at needling site	• Mild transient pain not at needling site	• Generalized muscle pain
• Reactive pain at other body sites	• Chest pain / tightness	• Other / unspecified pain / aches
Gastrointestinal / gynaecological system		
• Nausea	• Tiredness next day after ten hours of diarrhoea (significant)	• Increased peristalsis
• Mild and transient nausea	• Stomach ache	• Loss of appetite
• Severe nausea	• Abdominal distension	• Other gastrointestinal complaints
• Vomiting	• Impaired bowel function	• Increased haemorrhage during menses
• Severe vomiting	• Digestive problems	• Menstrual problems
• Constipation	• Entero- / gastrospasm	
• Diarrhoea		
Cardiovascular system		
• Cardiovascular / circulatory problems	• Increase in blood pressure	• Tachycardia
• Depression of blood pressure	• Palpitation	• Other cardiac disturbances
Respiratory system		
• Asthma attack	• Breathing difficulties	• Bronchitis or airway problems
Generalized skin reactions		
• Dermatological problems	• Other dermatological phenomena	
Headache		
• Headache	• Headache for three days	• Severe headache or migraine
• Headache the next day	• Migraine attack	
Emotional interference		
• Aggressive behaviour	• Depressive mood	• Severe emotional outburst and anger at practitioner
• Anxiety	• Discomfort	• Fear
• Anxiety and panic (up to one hour)	• Restlessness or nervousness	• Grief / crying / tearful
• Significant panic with sensation of heat and sweatiness	• Disorientation, anxiety, nervousness, insomnia or emotional	• Needle phobia, anxiety and rage
• Severe panic / agitation / depression with anxiety	• Emotional /psychological reaction	• (Severe) nightmares
• Depressed emotional state or neurovegetative dystonia	• (Uncontrolled) euphoria	• Other mood swings
	• Significant emotional release (manic, relaxed, rage or confusion)	
Sleeping problems		
• Sleep disturbances	• Severe sleeping problems	• Insomnia
• Impaired sleep	• Severe sleeplessness	
Moxa caused adverse events		
• Burn injury	• Burns	• Blister following moxibustion
Needling malpractice		
• Left alone / unattended in the treatment room for too long	• Failure to remove needle(s)	
• Broken needle	• Forgotten / dropped needle	
• Stuck or bent needle	• Needle lost or forgotten	
Other or unclassified adverse events		
• Change of symptoms	• Nose bleeding	• Additional comments
• Illness	• Miscellaneous symptoms	• Other systematic symptoms
• Sick	• Haematuria on next day	• Other neurological problems
• (Systemic) infection	• Increased urinary frequency	• Others / unspecified / other (mild) adverse events
• Fever	• Concomitant diseases of recent appearance	• other negative reactions
• Angina	• Change of taste	• Unknown due to incomplete record form
• Eye irritation	• Change of weight / weight reduction	
• Irritated tongue		

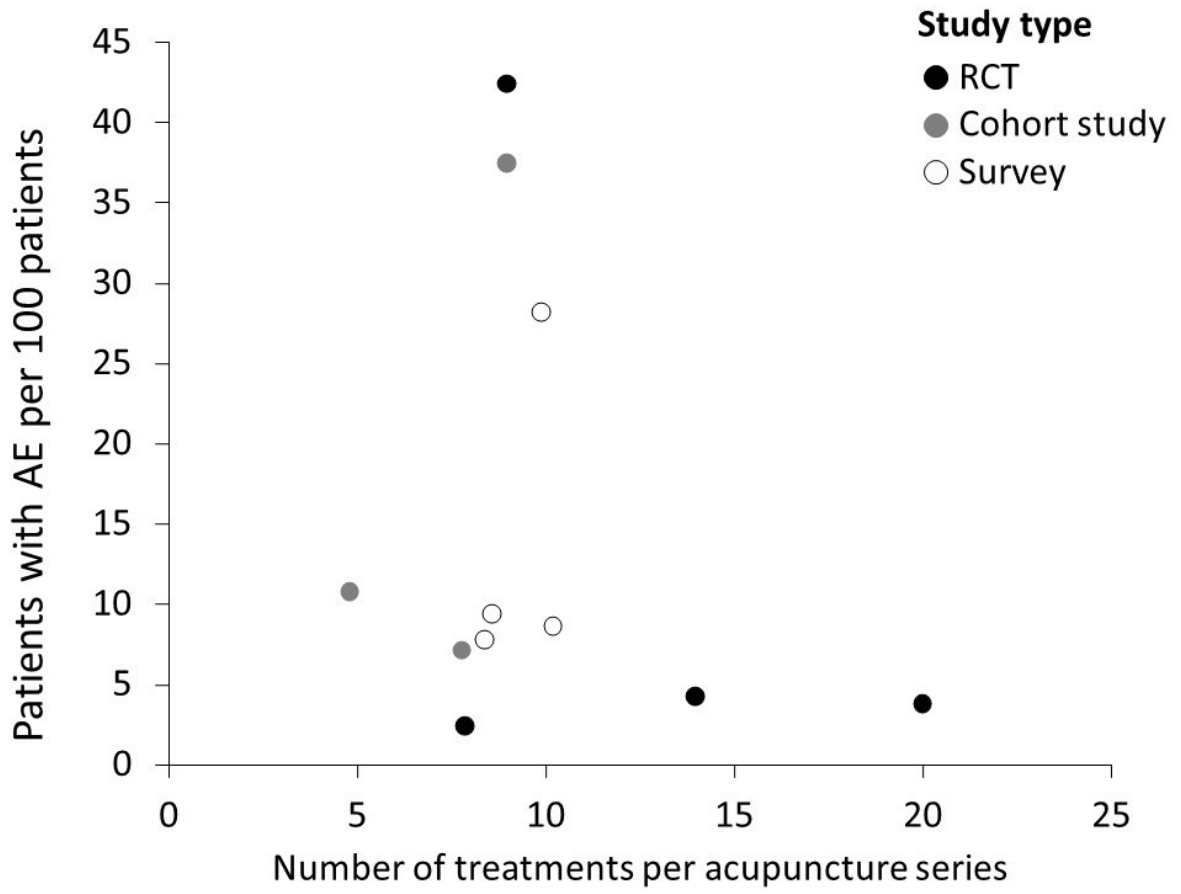
Online supplementary appendix S3: Categorization of adverse events

Subheadings represent the categories to which adverse events (AE) were assigned. AE descriptors extracted from the included publication are reported verbatim or in spirit in order to provide an overview of the different wordings concerning AE type and severity. Slashes indicate that expressions were also used separately. Terms in brackets indicate that such terms were not used in all of the descriptors with otherwise similar wording.

Study	AE definition (*direct quotes* with eventual comments)	Severity rating (*direct quotes* with eventual comments)
Chung 2015	*"Participants were asked the acupuncture AEs by acupuncturists using an open-ended question first, then the AcupAE. The open ended question asked if they had any discomfort during treatment and after the last few treatments."*	*"…mild AE required no treatment or resolved within 1 day, moderate AE lasted more than 1 day or relieved by non-prescription medication, severe AE required medical treatment."*
Da Silva 2014	*"Adverse effects were defined as 'any unusual, inconvenient or ill-effect, no matter how small, that is unintended and non-therapeutic', Examples were given to patients"; "We did not included 'aggravation of symptoms' because of the difficulty in judging whether the event was associated with acupuncture, was serious or not, and also because some practitioners believe that transient worsening is part of treatment."*	*"A 'serious event' was considered as one which needed further specific medical intervention or had interfered with the patient's normal life for at least the remainder of the day"*
Endres 2004	*"The ICH definition of an adverse event (AEs) is any untoward medical occurrence experienced by patients, temporally but not necessarily causally associated with the use of a drug or medical treatment…"*	*"… serious adverse event (SAEs) identified, according to the ICH, as an adverse event that results in a life-threatening condition or death, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity, including congenital anomaly/birth defects"*
Ernst 2003	*"A checklist was provided which mentioned haemorrhage, haematoma, infections, neurological abnormalities, fainting, vestibular symptoms, nausea, prolonged DeQi effect and increase of pain. Free space was provided to record other observed adverse effects. All therapists asked their patients with standardised open questions: during therapy, "How do you feel now?"; and before every subsequent therapy, "How did you feel after the last acupuncture therapy?". The therapists were asked to document 'possible septic syndrome' if fever and/or hypotension were observed in combination with local infection at one or more points that had been needled."*	SAE not defined
Furose 2017	*''…any untoward medical occurrence in a patient who underwent acupuncture therapy and which does not necessarily have a causal relationship with this treatment.''* In line with ICH but only selection list with AE likely related to acupuncture applied	*"…serious AE (pneumothorax, other organ injury, central nerve injury, peripheral nerve injury, suppurative arthritis, suppurative myositis, cellulitis, hepatitis B, hepatitis C, needle breakage and/or needle migration, accidental insertion, and other symptoms that practitioners regarded as serious)…"*
Leung 2009	*"A list of possible complications and adverse effects was used to check the events thoroughly. The list consisted of bleeding, obvious tissue/ organ damage, fainting, syncope, persistent needle pain, post-puncture tiredness, palpitation, exacerbation of symptoms nausea, dyspnea, convulsion, psychological symptoms, etc."*	SAE not defined *"no harmful complication was encountered"*
List 1992	*"In this paper, adverse event refers to any reaction to a treatment besides the intended treatment effect irrespective of any correlation between the treatment and the reaction."*	SAE not defined
Mac Pherson 2001	*"Practitioners were asked to record mild transient reactions to treatment, within one or more of three categories (systemic, aggravation, local)"*	*"…'significant adverse event' was defined as any event that was 'unusual, novel, dangerous, significantly inconvenient, or requiring further information'…"*
Mac Pherson 2004	*"For the purposes of this survey we did not define an adverse event but, instead, provided patients with a checklist of possible events. This and the overall questionnaire, while not formally validated, were developed from two practitioner surveys."*	*"In contrast, ''serious adverse events'' were predefined as those resulting in admission to hospital or being permanently disabling or life threatening"*
Mac Pherson 2005	*"Patients were asked to report short term reactions, by answering the question: 'Thinking about the visit at which you were given this form, did you experience during or immediately after your acupuncture any of the following?' We provided a checklist of possible short term reactions drawn from the results of two recently published practitioner surveys."*	SAE not defined
Melchart 1998	*„Der Fragebogen sollte, der Erfahrung der behandelnden Ärzte entsprechend vergleichsweise häufige Ereignisse erfassen, die aus Patientensicht im allgemeinen als unangenehm oder unerwünscht beurteilt werden"* English translation: The questionnaire was designed to reflect relatively frequent events that are, according to the physicians' experience, often experienced as unpleasant or adverse by the patient.	SAE not defined
Melchart 2004	*"…physicians had to report whether an adverse effect (defined as any adverse event possibly related to acupuncture) occurred. If this was the case, the adverse effect had to be specified. Predefined categories were bleeding, needling pain, hematoma, infection orthostatic problems, forgotten needles, and any other events."*	*"Serious adverse effects (defined as any adverse effects possibly related to acupuncture making treatment necessary or severely interfering with the patient's wellbeing, eg a pneumothorax or a nerve injury)…"*
Odsberg 2001	*"Negative side effect – a non-intended effect of the acupuncture treatment that the patient experiences as negative, i.e. haematoma and fainting."*	*"Complication – a non-intended effect of the acupuncture treatment that may threaten the patient's life, i.e. pneumothorax."*
Park 2009	*"Therefore, this study has surveyed to report on short-term reactions as well as de qi, side-effects, and the satisfaction of patients following acupuncture treatment.", "After explaining the purpose of the survey to the patients, we had them fill out a survey form querying their reactions…"*	*SAE not defined*

Park 2010	*"According to the World Health Organization (WHO), an AE is described as ''any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.'',* *"In the AE section, the reporter was asked to describe when the AEs appeared and disappeared, the type and details of the AE, and the treatment for the AE. Two (2) types of AE were identified: local AEs and systemic AEs….", "Local AEs included a broken or forgotten needle, hemorrhage, needle allergy, needle-site pain, hematoma, and a stuck or bent needle. Systemic AEs included drowsiness, fainting, fever, hypotension, nausea, vomiting, diarrhea, sweating, headache, discomfort, dizziness, anxiety and panic, seizure, insensibility, mental disturbance, pain, temporary paresthesia, pneumothorax, organ or tissue injury, hepatitis B/C, otitis externa, sepsis, central nerve injury, skin infection, or symptom aggravation."*	*"The International Conference on Harmonization guidelines define a serious AE as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is a congenital anomaly/birth defect.18 There were no serious AEs related to acupuncture in this study."*
Weiden-hammer 2008	*„Außerdem wurde gefragt: „Welche unerwünschten Wirkungen oder Komplikationen der Akupunktur sind aufgetreten?" Antwortoptionen waren hier: „Blutung", „Nadelschmerz", „Hämatom", „Infektionen", „Kreislaufprobleme", „vergessene Nadeln" und „andere" (mit Freitextfeld zur Beschreibung des Ereignisses)."* English translation: Furthermore it was asked „Which adverse effects or complications occurred through acupuncture?" Response options were: 'bleeding', 'needling pain', 'haematoma', 'infections', 'circulatory problems', 'forgotten needles' and 'others' (with free text for a description of the event)	*"Als schwerwiegende unerwünschte Therapiewirkungen waren alle Ereignisse zu bewerten, die a) möglicherweise in einem kausalen Zusammenhang mit der Akupunkturbehandlung standen und b) behandlungspflichtig waren oder/und den Patienten gravierend beeinträchtigten oder gefährdeten (z. B. Pneumothorax, Nervenläsion)."* English translation: Serious adverse treatment effects were defined as events that a) had a possibly causal relationship with the acupuncture treatment and b) required treatment and/or compromised or threatened the patient seriously (e.g. pneumothorax, nerve lesion).
Wen 2017	*"Adverse events, including pain, hematoma, perforation, bleeding, fainting, local infection, abscess, or breakage or retention of the needle after treatment, were recorded after every session."*	SAE not defined
White 2001	*"We defined an adverse event as 'any ill-effect, no matter how small, that is unintended and nontherapeutic'. This definition was used both in order to identify events that occurred through error but were not reactions to acupuncture, and in order to include minor events such as bleeding, not just serious events, even when these may have been an expected consequence of needling. We decided not to record unintended beneficial or pleasant events.", "…number of adverse events classified under specific headings…", "Some practitioners regard aggravation or drowsiness as a part of the response to treatment (the 'healing crisis'), and not as unintended 'adverse' events. Therefore, if a patient later improved substantially, respondents were instructed to convert the relevant mark in the box to an asterisk."*	*"Significant Event Report….to record any event that was 'unusual, novel, dangerous, significantly inconvenient or requiring further information'. Examples were provided, which included needling problems (broken or forgotten needle, moxa burns), systemic effects (faint, convulsion, drowsiness causing hazard e.g. on the road, severe nausea) and symptoms (unexpected or prolonged aggravation)."*
Witt 2009	*"At the end of each treatment cycle, all patients were asked to complete a standardised questionnaire and to document adverse events they associated with acupuncture (defined as adverse effects) in free text and, if necessary, the kind of treatment they had needed (self-treatment, medication/physician treatment, treatment in hospital). Adverse events without association to the acupuncture treatment were not documented."*	*"Patients who reported adverse effects which needed treatment, received from the study office an additional, more detailed standardised questionnaire concerning their most important adverse effect."*
Yamashita 1999	*"We defined AE as an unfavorable medical event that occurred during or after the treatment regardless of causal relationships [Beam 1992]"*	*"…no serious or severe cases of negligence such as pneumothorax or spinal cord injury were reported in the TCT Clinic But 2 cases identified from reports that required hospitalization / likely to have caused disability."*
Yamashita 2000	*"The acupuncturists meticulously observed the punctured region and general condition of the patients during and immediately after treatment. The patients were asked to report any pain or discomfort caused by needle insertion. In the interview after each treatment session, the acupuncturists asked the patients, "Did you feel any discomfort during today's treatment session, or do you have now such a feeling that did not exist before the treatment session? Please tell me every slight discomfort even if you don't think it is a problem." A similar question was asked at the patient's next visit, "Did you feel any discomfort that may have had something to do with the previous treatment, after you left our clinic?"*	*"Details recorded on the report form included … severity or magnitude of symptom, and treatment for the reaction.",* *"All reactions were mild and transient."* *"No medical care was required for any of these reactions."*
Zhao 2011	*"AE is defined as an unfavourable medical event that occurs during or after the treatment regardless of causal relationship",* *"AE and SAE were defined a priori from the literature and the State Food and Drug Administration (SFDA) in China."*	*"Serious adverse effects (SAEs) refers to those that caused hospitalisation, extended duration of hospitalisation, disability, impaired ability to work, death or were life threatening, resulting in events such as congenital malformations in the process of the clinical trials."*

Online supplementary appendix S4: Definition of adverse events with respective severity ratings as direct quotes from the included manuscripts



Online supplementary appendix S5: Independence of incidences of adverse events per patient from the number of treatments per acupuncture series and study type

Scatterplot of the number of treatments applied within an acupuncture series against the observed adverse events (AE) incidence as patients with AE per 100 patients

Study	Total number of patients	Risk as patients with AE per 100 patients [95%-CI]									
		Bleeding	Needle sit pain	Other local AE	Vegetative reaction	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal / gynaecologcial system	Unclassified AE
List 1992	29		44.83 [27.46; 62.87]		58.62 [40.52; 75.59]	93.10 [81.26; 99.30]	37.93 [21.45; 55.99]	27.59 [13.14; 44.96]		17.24 [5.94; 32.83]	3.45 [0.00; 12.99]
Chung 2015	59	15.25 [7.30; 25.45]	32.20 [20.99; 44.57]	35.59 [23.97; 48.14]	13.56 [6.10; 23.38]		5.08 [0.99; 12.08]	11.86 [4.94; 21.26]		5.08 [0.99; 12.08]	3.39 [0.33; 9.47]
Wen 2016	120	0.83 [0.00; 3.24]	2.50 [0.48; 6.04]						0.83 [0.00; 3.24]		
Melchart 1998	121	3.31 [0.88; 7.21]	14.05 [8.46; 20.78]	1.65 [0.16; 4.68]	8.26 [4.05; 13.81]	10.74 [5.88; 16.85]	2.48 [0.48; 5.99]	0.83 [0.00; 3.21]	0.83 [0.00; 3.21]	4.13 [1.33; 8.39]	
Leung 2009	254	2.36 [0.86; 4.58]									
Yamashita 2000	391		0.26 [0.00; 1.00]	1.02 [0.27; 2.26]	11.76 [8.76; 15.14]	2.81 [1.41; 4.68]	0.77 [0.15; 1.87]				
Ernst 2003	409	25.18 [21.10; 29.50]	8.07 [5.63; 10.90]	0.24 [0.00; 0.96]	6.36 [4.20; 8.92]	0.98 [0.26; 2.16]	6.11 [4.00; 8.64]	4.89 [3.01; 7.19]		1.96 [0.84; 3.52]	17.85 [14.29; 21.70]
Zhao 2011	1968	3.40 [2.65; 4.25]	0.05 [0.00; 0.20]		0.10 [0.01; 0.29]		0.05 [0.00; 0.20]			0.05 [0.00; 0.20]	
Furuse 2017	2180	12.80 [11.43; 14.23]	6.24 [5.26; 7.29]			1.06 [0.67; 1.53]					1.10 [0.71; 1.58]
Weidenhammer 2008 patients	5998	0.48 [0.32; 0.67]	0.32 [0.19; 0.47]	0.32 [0.19; 0.47]	2.72 [2.32; 3.14]	0.80 [0.59; 1.04]	0.90 [0.68; 1.16]	0.47 [0.31; 0.66]	0.95 [0.72; 1.21]	0.62 [0.43; 0.83]	0.47 [0.31; 0.66]
MacPherson 2004	6348	0.58 [0.41; 0.79]	1.86 [1.54; 2.21]	0.36 [0.23; 0.53]	4.69 [4.19; 5.23]	1.20 [0.94; 1.48]	0.87 [0.65; 1.11]	0.65 [0.46; 0.86]	0.17 [0.09; 0.29]	0.96 [0.74; 1.22]	0.38 [0.24; 0.54]
Melchart 2004	97733	4.56 [4.43; 4.70]	3.28 [3.17; 3.39]	0.18 [0.15; 0.20]	0.48 [0.44; 0.53]	0.12 [0.10; 0.14]					0.33 [0.29; 0.36]
Endres 2004	190924	5.18 [5.08; 5.28]	0.05 [0.04; 0.06]	24.51 [24.31; 24.70]	0.70 [0.67; 0.74]	1.31 [1.26; 1.36]		0.08 [0.07; 0.10]			0.07 [0.05; 0.08]
Witt 2009	229230	6.15 [6.05; 6.24]	0.45 [0.43; 0.48]	0.60 [0.57; 0.63]	0.30 [0.28; 0.33]	0.40 [0.38; 0.43]	0.26 [0.24; 0.28]	0.26 [0.24; 0.28]	0.76 [0.72; 0.79]	0.22 [0.20; 0.24]	0.11 [0.10; 0.12]
Weidenhammer 2008 therapists	503397	4.84 [4.78; 4.90]	3.95 [3.90; 4.01]	0.15 [0.14; 0.16]	0.08 [0.07; 0.08]	0.08 [0.07; 0.09]				0.01 [0.01; 0.02]	0.26 [0.25; 0.28]
Fixed effect		5.09 [5.05; 5.13]	1.81 [1.78; 1.84]	1.85 [1.83; 1.88]	0.25 [0.24; 0.26]	0.29 [0.28; 0.30]	0.28 [0.26; 0.31]	0.18 [0.17; 0.19]	0.74 [0.71; 0.77]	0.06 [0.05; 0.06]	0.19 [0.18; 0.20]
Random effect		4.67 [2.08; 8.22]	3.75 [0.74; 8.94]	2.79 [0.02; 10.01]	1.95 [0.40; 4.63]	1.48 [0.00; 5.90]	1.45 [0.07; 4.51]	0.69 [0.02; 2.34]	0.60 [0.21; 1.20]	0.60 [0.04; 1.81]	0.57 [0.01; 1.95]
tau^2		0.0008	0.0085	0.0494	0.0012	0.0017	0.0018	0.0004	0.0005	0.0008	0.0003
I^2		99.4% [99.3%; 99.5%]	99.9% [99.9%; 99.9%]	100.0% [100.0%; 100.0%]	99.7% [99.7%; 99.7%]	99.8% [99.8%; 99.8%]	96.3% [94.6%; 97.5%]	98.1% [97.4%; 98.7%]	92.6% [85.7%; 96.2%]	99.3% [99.1%; 99.4%]	99.0% [98.7%; 99.2%]
p-value Q-test		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Study	Total number of patients	Risk as patients with AE per 100 patients [95%-CI]								
		Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
List 1992	29			41,38 [24,41; 59,48]				20,69 [8,19; 37,03]		
Chung 2015	59	13.56 [6.0980; 23.38]			1,69 [0,00; 6,52]	0,00 [0,00; 1,62]				
Wen 2016	120									
Melchart 1998	121		0.83 [0.00; 3.21]				0,83 [0,00; 3,21]			
Leung 2009	254									
Yamashita 2000	391	0.51 [0.0485; 1.46]								
Ernst 2003	409	0.49 [0.0463; 1.40]	0.49 [0.05; 1.40]	0,24 [0,00; 0,96]			0,98 [0,26; 2,16]			0,24 [0,00; 0,96]
Zhao 2011	1968			0,10 [0,01; 0,29]						
Furuse 2017	2180	0.05 [0.0000; 0.18]				0,60 [0,32; 0,96]			0,96 [0,60; 1,42]	
Weidenhammer 2008 patients	5998	1.37 [1.0889; 1.68]	0.60 [0.42; 0.81]	0,35 [0,22; 0,52]				0,13 [0,06; 0,24]		0,07 [0,02; 0,15]
MacPherson 2004	6348	1.21 [0.9585; 1.50]				1,04 [0,81; 1,30]	1,24 [0,99; 1,53]	0,74 [0,54; 0,97]	0,44 [0,29; 0,62]	
Melchart 2004	97733	0.04 [0.0275; 0.05]				0,25 [0,22; 0,28]				
Endres 2004	190924					0,00 [0,00; 0,00]	0,04 [0,03; 0,05]	0,04 [0,03; 0,05]	0,00 [0,00; 0,00]	
Witt 2009	229230	0.52 [0.4944; 0.55]	0.27 [0.25; 0.29]	0,08 [0,07; 0,09]	0,09 [0,08; 0,10]	0,01 [0,00; 0,01]	0,09 [0,08; 0,11]	0,04 [0,03; 0,05]	0,01 [0,00; 0,01]	0,02 [0,01; 0,02]
Weidenhammer 2008 therapists	503397	0.03 [0.0287; 0.04]	0.42 [0.40; 0.43]			0,28 [0,27; 0,30]	, 0,0197 [0,02; 0,02]			
Fixed effect		0.12 [0.11; 0.13]		0,09 [0,08; 0,10]	0,09 [0,08; 0,10]	0,11 [0,11; 0,12]	0,04 [0,04; 0,04]	0,05 [0,04; 0,05]	0,00 [0,00; 0,01]	0,02 [0,01; 0,02]
Random effect		0.51 [0.03; 1.55]	0.40 [0.24; 0.61]	0,38 [0,00; 4,79]	0,35 [0,00; 35,67]	0,22 [0,01; 0,67]	0,20 [0,00; 0,81]	0,16 [0,00; 0,91]	0,14 [0,00; 1,16]	0,04 [0,00; 0,26]
tau²		0.0012	0.0001	0.0011	0.0029	0.0009	0.0002	0.0001	0.0002	0.0001
I²		99.6% [99.6%; 99.7%]	96.4% [93.9%; 97.9%]	94.6% [90.2%; 97.1%]	= 58.2% [0.0%; 90.1%]	99.7% [99.7%; 99.8%]	98.7% [98.2%; 99.1%]	97.1% [95.3%; 98.2%]	98.3% [97.3%; 99.0%]	69.0% [0.0%; 91.0%]
p-value Q-test		< 0.0001	< 0.0001	< 0.0001	0.1221	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0398

Online supplementary appendix S6: Risks for different types of adverse events per 100 patients undergoing an acupuncture series as reported in single studies

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses displayed in table 4

Study	Total number of treatments	Risk as treatments with AE per 100 treatments [95%-CI]									
		Bleeding	Pain	Other local AE	Vegetative nervous system	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal /gynaecologcial AE	Unclassified AE
Yamashita 2000	1441	45.45 [42.89; 48.03]	15.75 [13.92; 17.68]	0.90 [0.48; 1.46]	4.72 [3.69; 5.87]	1.11 [0.63; 1.72]	0.35 [0.11; 0.72]		0.07 [0.00; 0.27]		
daSilva 2014	13884	4.11 [3.79; 4.45]	3.02 [2.74; 3.31]	0.43 [0.33; 0.55]	0.02 [0.00; 0.05]		0.01 [0.00; 0.03]	0.11 [0.06; 0.17]		0.04 [0.01; 0.07]	
Melchart 1998	1200	0.33 [0.09; 0.74]	4.17 [3.11; 5.37]	0.17 [0.02; 0.48]	2.58 [1.76; 3.56]	1.75 [1.09; 2.57]	0.25 [0.05; 0.61]	0.08 [0.00; 0.33]	0.08 [0.00; 0.33]	0.42 [0.13; 0.86]	
MacPherson 2005	9408	4.72 [4.30; 5.16]	12.27 [11.61; 12.94]	0.26 [0.16; 0.37]	27.87 [26.97; 28.78]	1.75 [1.50; 2.03]		0.35 [0.24; 0.48]	4.49 [4.08; 4.91]	1.18 [0.97; 1.41]	0.35 [0.24; 0.48]
Furuse 2017	14039	3.16 [2.88; 3.46]	1.25 [1.07; 1.44]	0.09 [0.04; 0.14]	0.63 [0.51; 0.77]	0.20 [0.13; 0.28]	0.09 [0.05; 0.15]	0.07 [0.03; 0.12]		0.10 [0.05; 0.16]	0.20 [0.13; 0.28]
Ernst 2003	3535	5.18 [4.47; 5.93]	1.30 [0.95; 1.70]	0.08 [0.02; 0.21]	2.46 [1.98; 3.00]	0.25 [0.12; 0.45]	1.08 [0.76; 1.44]	1.44 [1.08; 1.86]		0.34 [0.17; 0.56]	5.46 [4.74; 6.23]
Odsberg 2001	9277	18.44 [17.66; 19.24]	0.08 [0.03; 0.14]	0.05 [0.02; 0.11]	1.42 [1.19; 1.67]	2.33 [2.03; 2.65]	0.18 [0.11; 0.28]	0.01 [0.00; 0.04]		0.02 [0.00; 0.06]	0.06 [0.02; 0.13]
Yamashita 1999	65482	0.03 [0.02; 0.05]	0.01 [0.00; 0.02]	0.00 [0.00; 0.01]	0.00 [0.00; 0.01]	0.00 [0.00; 0.01]	0.01 [0.00; 0.02]	0.00 [0.00; 0.01]		0.01 [0.00; 0.02]	0.00 [0.00; 0.01]
Park 2009	1095	8.40 [6.83; 10.12]	3.38 [2.39; 4.53]		3.11 [2.16; 4.21]		0.82 [0.37; 1.44]	1.46 [0.84; 2.26]			0.46 [0.14; 0.94]
Leung 2009	2000	0.40 [0.17; 0.72]									
Park 2010	3071	1.95 [1.49; 2.47]	0.49 [0.27; 0.77]	0.10 [0.02; 0.24]	0.75 [0.66; 0.85]	0.07 [0.01; 0.19]	0.03 [0.00; 0.13]	0.26 [0.11; 0.47]		0.03 [0.00; 0.13]	0.03 [0.00; 0.13]
White 2001	31822	3.09 [2.90; 3.28]	1.15 [1.04; 1.27]	0.10 [0.07; 0.13]	4.73 [4.50; 4.95]	0.98 [0.87; 1.09]	0.01 [0.00; 0.03]	0.00 [0.00; 0.01]		0.02 [0.01; 0.04]	0.46 [0.39; 0.54]
MacPherson 2001	34407	2.08 [1.93; 2.23]	1.24 [1.12; 1.35]	0.01 [0.00; 0.02]	4.73 [4.50; 4.95]	2.83 [2.66; 3.01]	0.63 [0.55; 0.71]		0.51 [0.44; 0.59]	0.31 [0.25; 0.37]	0.86 [0.76; 0.96]
Fixed effect		1.87 [1.80; 1.93]	0.82 [0.78; 0.87]	0.05 [0.04; 0.06]	1.08 [1.04; 1.13]	0.58 [0.55; 0.62]	0.09 [0.07; 0.10]	0.03 [0.02; 0.04]	0.96 [0.87; 1.05]	0.08 [0.07; 0.09]	0.23 [0.20; 0.25]
Random effect		4.92 [1.18; 11.01]	2.43 [0.63; 5.35]	0.13 [0.04; 0.27]	2.24 [0.21; 6.35]	0.84 [0.26; 1.75]	0.20 [0.05; 0.46]	0.19 [0.02; 0.55]	0.73 [0.00; 5.02]	0.15 [0.03; 0.38]	0.47 [0.03; 1.46]
tau^2		0.0169	0.0095	0.0004	0.0213	0.0055	0.0011	0.0008	0.0085	0.0008	0.0025
I^2		99.9% [99.9%; 99.9%]	99.8% [99.8%; 99.8%]	96.4% [94.9%; 97.4%]	99.9% [99.9%; 99.9%]	99.7% [99.6%; 99.7%]	98.4% [97.9%; 98.8%]	97.5% [96.6%; 98.2%]	99.5% [99.4%; 99.7%]	98.2% [97.6%; 98.6%]	99.4% [99.2%; 99.5%]
p-value Q-test		< 0.0001	< 0.0001	0.0001	< 0.0001	< 0.0001	0.0001	< 0.0001	0.0001	0.0001	0.0001

Study	Total number of treatments	Risk as treatments with AE per 100 treatments [95%-CI]								
		Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
Yamashita2000	1441	0.14 [0.01; 0.40]				0.62 [0.28; 1.10]				
daSilva2014	13884					0.24 [0.16; 0.33]				
Melchart1998	1200		0.08 [0.00; 0.33]				0.08 [0.00; 0.33]			
MacPherson2005	9408						0.67 [0.51; 0.84]			
Furuse2017	14039	0.01 [0.00; 0.03]	0.01 [0.00; 0.04]			0.10 [0.05; 0.16]			0.17 [0.11; 0.25]	
Ernst2003	3535	0.06 [0.01; 0.16]	0.06 [0.01; 0.16]	0.03 [0.00; 0.11]			0.11 [0.03; 0.25]			0.03 [0.00; 0.11]
Odsberg2001	9277	0.05 [0.02; 0.11]		0.01 [0.00; 0.04]			0.04 [0.01; 0.10]			
Yamashita1999	65482					0.04 [0.03; 0.06]	0.01 [0.00; 0.02]		0.01 [0.00; 0.02]	
Park2009	1095									
Leung2009	2000									
Park2010	3071	0.03 [0.00; 0.13]		0.10 [0.02; 0.24]		0.10 [0.02; 0.24]				
White2001	31822	0.11 [0.08; 0.15]		0.00 [0.00; 0.01]		0.15 [0.11; 0.19]	0.01 [0.00; 0.02]		0.00 [0.00; 0.01]	
MacPherson2001	34407	0.00 [0.00; 0.01]		0.00 [0.00; 0.01]		0.01 [0.00; 0.02]	0.01 [0.00; 0.03]		0.00 [0.00; 0.01]	
Fixed effect		0.03 [0.02; 0.05]	0.02 [0.01; 0.05]	0.01 [0.00; 0.01]		0.06 [0.05; 0.08]	0.03 [0.02; 0.03]		0.01 [0.01; 0.02]	
Random effect		0.04 [0.01; 0.10]	0.03 [0.00; 0.13]	0.01 [0.00; 0.04]		0.12 [0.02; 0.28]	0.08 [0.00; 0.27]		0.02 [0.00; 0.18]	0.03 [0.00; 0.11]
tau²		0.0002	0.0001	0.0001		0.0002	0.0004		0.0001	
I²		90.3% [82.5%; 94.6%]	21.2% [0.0%; 91.8%]	58.1% [0.0%; 84.4%]		95.1% [92.0%; 96.9%]	96.8% [95.1%; 97.9%]		95.0% [90.3%; 97.5%]	
p-value Q-test		0.0001	0.2811	0.0489		0.0001	0.0001		0.0001	

Online supplementary appendix S7: Risks for different types of adverse events per 100 treatments as reported in single studies

Summary risk estimates of adverse events (AE) derived from random effects meta-analyses displayed in table 4