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

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Page	3 of 48 BMJ Open
1	Abstract
2 3	Objective
3 4 5	Overview on risks for acupuncture related adverse events (AE).
6	Design
7 8	Systematic review and meta-analysis of prospective studies.
9 10	Data sources
11 12	Pubmed, Scopus, and EMBASE from inception date to September 15, 2019.
13 14	Eligibility criteria for selecting studies
15	Prospective studies assessing AE caused by needle acupuncture in humans as primary outcome published in English
16 17	or German
18 19	Data extraction and synthesis
20	Two independent researchers selected articles, extracted the data and assessed study quality. Overall risks and risks
21 22	for different AE categories were obtained from random effects meta-analyses.
23 24	Main outcomes
25 26	Overall risk for minor AE and serious AE (SAE) per patients and per treatments
20 27 28	Results
29	Out of 7679 screened articles 22 reporting on 21 studies were included. Meta-analyses suggest at least one AE
30 31	occurring in 9.31% (95%-CI 5.10 to 14.62; 11 studies) of patients undergoing an acupuncture series and in 7.57% (95%-
32	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)
33 34	per 10,000 patients and 7.98 (95%-Cl 1.39 to 20.00; 14 studies) per 1 million treatments, for AE requiring treatment
35	1.14 (95%-Cl 0.00 to 7.37; eight studies) per 1000 patients. Heterogeneity was substantial (I ² >80%). On average 9.4 AE
36 37	occurred in 100 treatments of which half were bleeding, pain, or flare at the needle site argued to represent intended
38	acupuncture reaction. AE definitions and assessments varied largely.
39 40	Conclusion
41 42	Acupuncture can be considered among the safer treatments in medicine. SAE are rare, and most common minor AE
43	are very mild. AE requiring medical management are uncommon, but necessitate medical competence to assure
44 45	patient safety. Clinical and methodological heterogeneity call for standardized AE assessments tools, clear criteria for
45 46	differentiating acupuncture related AE from therapeutically desired reactions, and identification of patient related risk
47 48	factors for AE.
49	PROSPERO registration number
50 51	CRD42020151930
52	
53 54	
55	Keywords
56 57	Adverse effects, adverse reactions, meta-analysis, safety, risk, pneumothorax
58	
59 60	

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

2 Acupuncture describes the insertion of fine needles at defined points on the patients' body for therapeutic or 3 preventive purposes. It is used worldwide with growing popularity. In the EU acupuncture was identified as the most 4 5 frequently provided method of complementary and alternative medicine (CAM) with 80,000 physicians and 16,380 6 non-medical practitioners.(1) In the UK alone 2.3 million traditional acupuncture treatments are carried each year.(2) 7 In the US the number of acupuncturists doubled between 2002 and 2012.(3) The effectiveness of acupuncture is 8 9 supported by level 1a evidence e.g. for chronic musculoskeletal pain and headache, (4-6) post-operative pain, (7, 8) 10 post-operative nausea and vomiting,(9) as well as allergic rhinitis.(10) Furthermore, promising evidence exists for its 11 12 potential role in the treatment of a large number of additional indications such as stroke rehabilitation,(11) 13 depression,(12) aromatase inhibitor induced arthralgia,(13) and asthma.(14) Thus, acupuncture offers a non-14 15 pharmacological treatment option for various highly prevalent conditions with great disease burden and significant 16 health economic impact. Long-term pharmacological treatment of these conditions is often associated with substantial 17 18 side effects.(15, 16) Consequently, also risk estimates on acupuncture related adverse events (AE) are required for 19 evidence-based risk benefit considerations that are essential for clinical decision making. 20

21 However, uncertainty remains about acupuncture safety. AE related to acupuncture are repeatedly and controversially 22 discussed both in scientific literature as well as in public media. An overview of systematic reviews in 2017 (17) 23 24 illustrates that many of the previous reviews on the safety of acupuncture just summarized case reports or case series. 25 In turn, those reviews including studies that do allow for AE frequency estimation, such as cohort studies and large 26 27 RCTs, mostly only addressed certain types of AE, particular patient groups, restricted acupuncture regimens, or certain 28 countries. These data are surely important for clinical decision making in particular cases, but leave the overall risk of 29 30 acupuncture related AE in the general population obscure. Additionally, debate exists about differentiating AE from 31 therapeutically intended reactions that are claimed to form part of the acupuncture treatment. For example, 32 33 international consensus exists that aggravation of symptoms represents an AE, since disease burden increases, 34 although transient worsening of symptoms followed by long-term improvements can be interpreted as a so called 35 healing crisis in complementary and alternative medicine.(18) In contrast, such consensus is still missing for local 36 37 reactions such as small bleedings upon needle withdrawal, needling pain, and flare around the needling site. These 38 are also referred to as beneficial signs by acupuncture experts and in standard text books and have been linked to 39 40 neurophysiological mechanisms of acupuncture, suggesting that quality and intensity of these events should be 41 considered when classifying them as AE.(19-21) 42

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

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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

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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)

11 12 In- and exclusion criteria

13 We included articles reporting on prospective studies assessing AE associated with needle acupuncture involving 14 manual or electrical stimulation combined with or without moxibustion in humans as their primary outcome. Only 15 16 articles published in English or German were included. Publications on assessments of acupuncture point injection 17 therapies or non-penetrating acupuncture point stimulation such as laser acupuncture, acupressure or transcutaneous 18 19 electrical nerve stimulation (TENS) were excluded. We also excluded articles reporting solely on moxibustion or 20 restricted acupuncture regimens such as press-needle, auricular or one-point acupuncture. Trials focusing just on one 21 22 type of acupuncture related AE or just on a narrowly defined patient population were excluded. 23

24 <u>Article selection and data extraction</u> 25

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.

30 Estimates of overall risks and risks for each reported type of AE were extracted as absolute number of patients with 31 AE per total number of patients and treatments with AE per total number of treatments. Data concerning AE from 32 33 sham- or placebo-acupuncture treatments were not extracted. The different types of AE were assigned to one of the 34 following categories: bleeding, local pain, other local AE, distant pain, central nervous system, peripheral nervous 35 36 system, vegetative nervous system, motor system, gastrointestinal / gynaecological system, cardiovascular system, 37 respiratory system, generalized skin reactions, headache, emotional interference, sleeping problems, AE related to 38 39 moxibustion, needling malpractice, aggravation of symptoms, other or unclassified AE (online supplementary 40 appendix S3). 41

42 Following the differentiation between AE and adverse drug reactions (ADR) defined by the International Conference 43 on Harmonization (ICH) of Good Clinical Practice, (25) articles were classified into reports on adverse events 44 45 irrespective of their causal relationship to acupuncture and adverse reactions for which a causal relationship was a 46 reasonable possibility. Serious adverse events (SAE) were reported as indicated in the included articles as in 47 48 accordance with the ICH-criteria. These include any untoward medical occurrence that at any dose results in death, is 49 life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization, results in persistent or 50 51 significant disability / incapacity, or is a congenital anomaly / birth defect.(25) Causality assessment of SAE was 52 performed by independent acupuncture therapists who were medical doctors who received more than 300 hours of 53 acupuncture training and with more than ten years of intensive acupuncture practice. As the basis of this assessment 54 55 was limited to incomplete information provided in the articles lacking e.g. time references, categories of SAE causality 56 were reduced to possibly or unlikely related to acupuncture or unclassifiable. 57

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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 ($\geq 1/10$ patients), common ($\geq 1/100$ to < 1/10), uncommon ($\geq 1/1,000$ to < 1/100), rare ($\geq 1/10,000$ 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.

14 <u>Risk of bias assessment</u>15

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, casecontrol 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.

25 Data analysis

26 Data were analysed using the package meta implemented in R.(28) Pooled estimates with 95% confidence intervals 27 28 (CI) for overall AE risk and risks of different types of AE were obtained from proportion meta-analyses. Random effects 29 models were calculated by the Hartung-Knapp method with arcsine transformation of proportions. Cochran Q test, 30 31 and I² statistics were used to assess the heterogeneity of included studies. Analysis were performed for the overall 32 risks as well as the risks for the different types of AE given as the number of patients with AE per total number of 33 34 patients undergoing an acupuncture series and as the number of treatments with AE per total number of treatments 35 performed. AE that were reported separately in the articles, but that were allocated to the same AE category, were 36 37 treated as they had occurred in different patients or treatments, respectively. Sensitivity analyses were performed for 38 studies that explicitly only reported about AE that had, at the discretion of the assessors', a causal relationship to 39 acupuncture treatments. 40

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.

51 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

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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)

14 Study characteristics are provided in table 1. The four largest trials with one to five hundred thousand patients treated 15 in over 750 thousand acupuncture sessions were cohort studies performed as part of the German Model Projects on 16 17 Acupuncture (Modellvorhaben Akupunktur).(31, 39, 44, 47) Three nationwide surveys from the UK (described in four 18 articles),(36-38, 46) one in-house surveillance report from Japan (49) and one summary of AE assessments nested 19 20 within three Chinese RCTs (50) included two to six thousand patients receiving over 30 thousand treatments, 21 respectively. In three surveys, two from South-Korea, (42, 43) one from Japan, (33) and one from Brazil, (30) around 22 23 one to two thousand patients were included and treated in up to 14 thousand acupuncture sessions. One nationwide 24 survey conducted in Sweden reported on the risk of AE based on data from over nine thousand acupuncture 25 26 sessions.(41) In seven studies less than 500 patients receiving maximum 3.5 thousand treatments were included; four 27 AE assessments nested within RCTS or clinical trials from China, (34, 45) Hong-Kong, (29) and Sweden, (35) one Japanese 28 29 (48) and one German survey (32) as well as one German cohort study.(40) In most studies acupuncture was used to 30 treat pain in middle aged patients. In six articles no details on the patients' condition were provided. (32, 33, 38, 41, 31 32 46, 48) Two articles reported explicitly on short-term AE after one particular treatment only. (37, 43) All but five articles 33 provided sufficient information to infer that acupuncturists had a firm medical background and / or had received 34 intensive acupuncture training. (32, 34, 35, 40, 41) One German survey also included "other practitioners" most likely 35 36 non-medical practitioners (Heilpraktiker) with non-standardized acupuncture training.(32) 37

Eight articles described AE reported by patients only (29, 30, 35-37, 43, 44, 47) and seven articles AE reported by 38 39 acupuncturists only. (31, 38, 39, 42, 44, 46, 49) As before said Weidenhammer et al. described therapists' and patients' 40 41 reports on AE separately. (44) Zhao et al. combined the AE reports from patients and acupuncturists. (50) In five articles 42 it was explicitly stated that acupuncturists recording the AE also queried their patients about any uncomfortable 43 experience during or after treatment.(32-34, 41, 48) In two trials AE were documented by an independent 44 45 assessor.(40, 45) In eight of the 22 included articles AE were reported irrespective of their relationship to 46 acupuncture, (29, 31, 32, 35, 38, 46, 49, 50) while descriptions of AE assessments in twelve articles suggest that only 47 48 AE related to the acupuncture treatment were documented, (30, 33, 34, 36, 37, 40-42, 44, 47, 48) and one article did 49 not provide information about the AE definition.(43) Further discrepancies were found in definitions of certain 50 51 reactions as therapeutically intended. For example, da Silva et al. did not count aggravation of symptoms as AE, 52 because of difficulties in determining causality as well as severity and because of common notion among practitioners 53 54 that transient worsening forms part of the acupuncture treatment. (30) In contrast White et al. reported observations 55 of aggravated symptoms as AE, but only those that were not followed by substantial improvements.(46) In contrast, 56 the other articles did not specify aggravation of symptoms further. (31-33, 35, 36, 40, 44, 47, 48) In addition, Endres et 57 58 al. did report on erythema at the needling site (which was accounted for in the present analysis), but did not include 59 it in their overall AE incidence report, as this can also be regarded as desired acupuncture reaction.(31) 60

Page 9	9 of 48					Patients		Treat	BMJ (Jpen		Acupu	uncturists			AE assessme	ent
	1 st Author year	Country	Study type	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
1	Chung 2015	Hong- Kong	RCT	59 (46)*)	49 ± 10*)	Insomnia in major depressive disorder	531	9 /3w	14	EA	n.i.	TCM doctors	n.i.	> 3 a	Р	SL & OQ any AE	after 3rd, 6th, 9th treatment
2 3	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.	Р	SL & OQ AE related to acu.	after each treatment
4	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.	А	SL & OQ any AE	after last treatment
5 6	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
7	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
8 9	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
9 10	List 1992	Sweden	RCT monocentric	29 (n.i.)	median 40**)	Craniomandibular disorder	арх. 174	≥6 /6-8w	12 avg.	MA & EA	1 (0)	n.i.	n.i.	n.i.	Р	SL & OQ any AE	after last treatment
11	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%	А	SL & OQ any AE	upon recognition
12 13	MacPherson 2004 ^A		Survey nationwide	6,348 (4,821)	52 ± 15	Musculoskeletal, psychological, general, neurological, gyne-	30,196	4.8		MA &	638	MD & physio-		< 10 a 58%		SL & OQ AE related to acu.	3 m after inclusion
14	MacPherson 2005 ^A	UK	private practices	9,408 (6,961)	51	cological, obstetric & respiratory conditions; wellbeing	9,408	1	n.i.	EA	(406)	therapists	> 3 a	≥ 10 a 42%	Р	SL imm. AE AE related to acu.	After the 1 st / one of the 1 st treatments
15 16	Melchart 1998	Germany	Cohort monocentric	121 (88)	54 ± 13	Mainly chronic pain	арх. 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
17	Melchart 2004	Germany	Cohort nationwide private clinics	97,733 (78,675)	55 ± 16	Chronic headache, osteoarthritis, LBP	арх. 760,000	7.8 ± 2.4	12.6 ± 5.1	n.i.	7050 (n.i.)	MD	> 140 h (19% > 350 h)	n.i.	А	SL & FT AE related to acu.	after last treatment
18 19	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
20	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	Р	n.i.	after 1 arbitrary treatment
21 22	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%	А	SL AE related to acu.	upon recognition
22				503,397 (40,5235)	54 ± 16		4.2 M	8.4 (2.9)			9918					SL & FT AE related to acu.	after last treatment
24	Weiden- hammer 2008	Germany	Cohort nationwide private clinics	882847 (n.i.)	n.i.	Chronic headache, LBP, osteoarthrosis (> 6 m)	7.9 M	n.i.	n.i.	n.i.	(3570)	MD	140 h (22% > 350 h)	n.i.	A	OQ - SAE only AE related to acu.	upon recognition
25 26	в			5,998 (5,072)	55 ± 15		apx. 51582 ^{#)}	8.6 (3.0)			9429 (n.i.)				Р	OQ AE related to acu.	after last treatment
27	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
28 29	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%	А	SL & OQ any AE	upon recognition
30 31	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	Р	OQ AE related to acu.	after last treatment
32	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%	А	OQ any AE	upon recognition
33 34	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
35 36	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	≥8a	> 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 P) 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%-Cl 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%-Cl 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.

	Number of		Number of AE	AE inciden	ice per 100 treatments	Bleeding, pain, flare at		
Study	treatments	total	excluding bleeding, pain & flare	total	excluding bleeding, pain & flare	needling site as % of all AE		
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

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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%-Cl 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%-Cl 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%-Cl 0.10 to 4.46) in 10,000 patients suffering from a SAE when undergoing an acupuncture series and 16.90 (95%-Cl 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	Melchart 2004	Causality	
- Death	unlikely	9	- Exacerbation of depression	possible	
- Fall or trauma, with or without fracture	possible	4	- Hypertensive crisis	possible	
- Acute general infection with hospitalization	unlikely	2	- Vasovagal reaction	possible	
 Allergic reaction to concomitant medication (atopy) 	possible	1	 Asthma attack with hypertension and angina 	possible	
 Stroke with hospitalization 	unlikely	3	- Pneumothorax	possible	
- Cardiovascular problems (hospital admission)	possible	3	Yamashita 1999	Causality	
- Intervertebral disk prolapse, pain exacerbation with hospital admission	unclassifiable	5	 Hospitalization of patient with asthma because of coughing 	possible	
- Malignant parotid tumor (hospital admission)	unlikely	1	- 1 case of deep burn that recovered after 2	possible	
- Hospitalization (unknown reasons)	unclassifiable	17	years		
Weidenhammer 2008 ther.	Causality	n	MacPherson 2004	Causality	
- Pneumothorax	possible	5	- Low back pain in breast cancer patient,	possible	
 Suicidiation in a patient with borderline syndrome 	unlikely	1	hospital admission, disappeared without medication, since then no more LBP		
 Hypertensive crisis 	possible	1	- Car crash 2d after acupuncture, very little	unlikely	
 Syncope (vasovagal reaction) 	possible	2	sleep the night before		
 Asthma attack in a patient with asthma 	possible	1	- Skin rash and feeling ill for several weeks	possible	
 Erysipelas (one in a patient with lymphedema) Circulatory collapse (one with uncontrolled 	possible	2	accompanied by decrease of ME		
defecation and one with vertigo and paresthesia)	possible	2	symptoms and feeling of catharsis (no treatment)		
- Circulatory reaction with amnesia	unlikely	1			
- Tonic-clonic seizures and ophistotonus	unlikely	1			
- Infection of the knee joint with E. coli bacteria	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 (I² 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;

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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) ic μ. 19 articles reμ. 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.

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-	Type of AE	Number of	Sum of	Risk as patient	s with AE per 100	patients [95%-CI]	Tau ²	Number of	Sum of	Risk as treatments	with AE per 100 tre	eatments [95%-CI]	Tau ²
_	Type of AE	studies	patients	overall	min	max	²	studies	treatments	overall	min	max	²
-	Bleeding	13	1038741	4.67	0.48	25.18	0.0008	13	190661	4.92	0.03	45.45	0.0169
	Diccum	15	1050741	[2.08; 8.22]	[0.32; 0.67]	[21.10; 29.50]	99.4%**	15	150001	[1.18; 11.01]	[0.02; 0.05]	[42.89; 48.03]	99.9%**
	Needle site pain	14	1038907	3.75	0.05	44.83	0.0085	12	188661	2.43	0.01	15.75	0.0095
				[0.74; 8.94]	[0.04; 0.06]	[27.46; 62.87]	99.9%**			[0.63; 5.35]	[0.00; 0.02]	[13.92; 17.68]	99.8%**
		10		2.79	0.15	35.59	0.0494		1075.00	0.13	0.00	0.90	0.0004
	Other local AE	10	1034610	[0.02; 10.01]	[0.14; 0.16]	[23.97; 48.14]	100.0%* *	11	187566	[0.04; 0.27]	[0.00; 0.01]	[0.48; 1.46]	96.4%**
	Vegetative	12	1036607	1.95	0.08	58.62	0.0012	12	188661	2.24	0.00	27.87	0.0213
	reaction	12	1030007	[0.40; 4.63]	[0.07; 0.08]	[40.52; 75.59]	99.7%**	12	100001	[0.21; 6.35]	[0.00; 0.01]	[26.97; 28.78]	99.9%**
	Aggravation of	11	1036760	1.48	0.08	93.10	0.0017	10	173682	0.84	0.00	2.83	0.0055
	symptoms		1050700	[0.00; 5.90]	[0.07; 0.09]	[81.26; 99.30]	99.8%**	10	175002	[0.26; 1.75]	[0.00; 0.01]	[2.66; 3.01]	99.7%**
	Central nervous	9	244553	1.45	0.05	37.93	0.0018	11	179253	0.20	0.01	1.08	0.0011
	system	5	21.000	[0.07; 4.51]	[0.00; 0.20]	[21.45; 55.99]	96.3%**		1,0100	[0.05; 0.46]	[0.00; 0.02]	[0.76; 1.44]	98.4%**
	Peripheral	8	433118	0.69	0.08	27.59	0.0004	10	152813	0.19	0.00	1.46	0.0008
	nervous system			[0.02; 2.34]	[0.07; 0.10]	[13.14; 44.96]	98.1%**			[0.02; 0.55]	[0.00; 0.01]	[0.84; 2.26]	98.0%**
	Distant pain	5	241817	0.60	0.17	0.95	0.0005	4	46456	0.73	0.07	4.49	0.0085
				[0.21; 1.20]	[0.09; 0.29]	[0.72; 1.21]	92.6%**			[0.00; 5.02]	[0.00; 0.27]	[4.08; 4.91]	99.5%**
	Gastrointestinal /	9	747559	0.60	0.01	17.24	0.0008	10	186125	0.15	0.01	1.18	0.0008
	gynaecologcial system	9	/4/559	[0.04; 1.81]	[0.01; 0.02]	[5.94; 32.83]	99.3%**	10	180125	[0.03; 0.38]	[0.00; 0.02]	[0.97; 1.41]	98.2%**
	-			0.57	0.07	17.85	0.0003			0.47	0.00	5.46	0.0025
	Unclassified AE	10	1036307	[0.01; 1.95]	[0.05; 0.08]	[14.29; 21.70]	99.0%**	9	172136	[0.03; 1.46]	[0.00; 0.01]	[4.74; 6.23]	99.4%**
	the sector de la	0	045745	0.51	0.03	13.56	0.0012	_	07502	0.04	0.00	0.14	0.0002
	Headache	9	845745	[0.03; 1.55]	[0.03; 0.04]	[6.10; 23.38]	99.6%**	7	97592	[0.01; 0.10]	[0.00; 0.01]	[0.01; 0.40]	90.3%**
	Cardiovascular	5	739155	0.40	0.27	0.83	0.0001	3	18774	0.03	0.01	0.08	0.0001
	system	5	/39155	[0.24; 0.61]	[0.25; 0.29]	[0.00; 3.21]	96.4%**	5	18/74	[0.00; 0.13]	[0.00; 0.04]	[0.00; 0.33]	21.2%
	Motor system	5	237634	0.38	0.08	41.38	0.0011	5	82112	0.01	0.00	0.03	0.0001
	wotor system	J	237034	[0.00; 4.79]	[0.07; 0.09]	[24.41; 59.48]	94.6%**	5	82112	[0.00; 0.04]	[0.00; 0.01]	[0.00; 0.11]	58.1%*
	Generalized skin	2	229289	0.35	0.09	1.69	0.0029	_					
	reaction	2	225205	[0.00; 35.67]	[0.08; 0.10]	[0.00; 6.52]	58.2%						
	Needling	7	1029871	0.22	0.00	1.04	0.0009	7	164146	0.12	0.01	0.62	0.0002
	malpractice	,	1025071	[0.01; 0.67]	[0.00; 0.00]	[0.81; 1.30]	99.7%**		101110	[0.02; 0.28]	[0.00; 0.02]	[0.28; 1.10]	95.1%**
	Emotional	6	930429	0.20	0.02	1.24	0.0002	7	155131	0.08	0.01	0.67	0.0004
	interference	-		[0.00; 0.81]	[0.02; 0.02]	[0.99; 1.53]	98.7%**	-		[0.00; 0.27]	[0.00; 0.02]	[0.51; 0.84]	96.8%**
	Sleeping	5	432529	0.16	0.04	20.69	0.0001	-					
	problems			[0.00; 0.91]	[0.03; 0.05]	[8.19; 37.03]	97.1%**			0.02	0.00	0.47	0.0004
	AE caused by	4	428682	0.14	0.00	0.96	0.0002	4	145750	0.02	0.00	0.17	0.0001
	moxibustion			[0.00; 1.16]	[0.00; 0.00]	[0.60; 1.42]	98.3%**			[0.00; 0.18]	[0.00; 0.01]	[0.11; 0.25]	95.0%**
	Respiratory	3	235637	0.04	0.02	0.24	0.0001	1	3535	0.03			
-	system			[0.00; 0.26]	[0.01; 0.02]	[0.00; 0.96]	69.0%*			[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

2 According to the inclusion criteria the study objective was clearly described in all articles (Figure 5, category A). Study 3 design was clear for all but one article, which stated that data were collected in the course of 11 clinical trials without 4 5 further specification.(34) Also, all but one AE assessment were free of a run in period. In one RCT the safety assessment 6 was initiated with a short delay.(35) Both irregularities were rated as unlikely to introduce bias into AE documentation. 7 8 High risk for selection bias (Figure 5, category B) was identified for the four RCTs and the AE assessment in 11 clinical 9 trials (23% of articles), due to exclusion of patients with comorbidities or bleeding tendency. In contrast, in all surveys 10 and cohort studies (77%) the risk for selection bias was rated as unclear due to an indistinct selection of therapists and 11 12 / or patients, inclusion of voluntarily participating acupuncturists or acupuncturists from specialized medical centres 13 only. Furthermore, none of the articles stated that patients were naive to acupuncture. Risk of bias due to study 14 15 withdrawal or drop-out (Figure 5, category C) was rated as low for all RCTs and two surveys, that only reported on 16 short-term AE (27%), (37, 43) and as high for one survey (5%), because treatment was ceased for 40% of patients with 17 18 AE.(42) For the remaining studies (68%) the risk of bias due to early treatment termination was rated as unclear, as 19 withdrawals and drop-outs due to AE were not reported. The risk of information bias regarding the safety outcome 20 21 (Figure 5, category D) was rated as high for one study (5%) because of an exclusive documentation of repeatedly 22 occurring AE (35) and as unclear for all remaining studies (95%). At this, AE reporting by patients or acupuncturists 23 24 instead of an independent assessor was classified as an unclear risk for social desirability bias. Using only a selection 25 list (33, 34, 37, 42) or only open questions as AE assessment tool,(47-49), lack of reporting on the AE assessment tool 26 27 (41, 43, 45) or the definition of the safety outcome, and selection of the time-point of the AE assessment (only directly 28 after treatment, (30, 31, 41, 45) only after the last treatment initiation, (35, 36, 39, 44, 47) solely upon recognition (38, 29 42, 46, 49)) were rated as possible but unclear sources of detection bias. Further risk of information bias (Figure 5, 30 31 category E) appeared to be unclear due to poor reporting of treatment details in all but seven studies (32%).(29, 35, 32 38, 39, 45, 48, 50) Bias arising from differential care, confounder assessment and statistical methods to control for 33 34 confounding (Figure 5, category F) was rated as low, as crude AE risk estimates and not relative risks with respect to a 35 comparator group were extracted. The risk of bias due to other statistical methods (Figure 5, category G) was also 36 37 rated as low, as reporting of AE incidence was clear and well-structured in all articles. 38

Bias due to conflict of interest (Figure 5, category H) might be present in four articles (18%) due to funding by 39 40 institution with direct interest in the public acknowledgement of acupuncture. (36, 37, 41, 42) In eight articles (36%) 41 funding or other conflicts of interest were not described. (32, 34, 35, 38, 40, 46, 48, 49) The ten remaining articles 42 43 (45%) included an explicit statement about funding by independent institutions and absence of other conflicts of 44 interest. 45

Discussion

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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 58 (bleeding, needle site pain, flare around the needle site).(21) SAE can be expected rarely in about every 10,000th 59 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 decisionmaking 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, 20 21 aggravation of symptoms, and AE related to the central nervous system (one to five out of 100 patients). This is in line 22 with other reviews (22, 57) also on auricular (58) and paediatric acupuncture. (56) All other types of minor AE can be 23 24 regarded as uncommon (1 to 7 out of 1000 patients), despite respiratory reactions that occurred very rarely (4 out of 25 10,000 patients). SAE most often reported were pneumothorax, strong cardiovascular or vasovagal reactions, and fall 26 27 or trauma with one to three cases in one million treatments. Several other sometimes fatal SAE repeatedly described 28 in case reports were not observed in the included studies; e.g. traumatic injuries of inner organs, local and systemic 29 30 infections, subarachnoid bleeding, infective endocarditis, and cardiac tamponade.(59-63) This is likely due to the fact 31 that acupuncturists in most of the studies were well trained, as SAE are claimed to be avoidable by proper acupuncture 32 33 training and practice. Concordantly, cases of acupuncture malpractice were uncommon in the included trials. 34

35 <u>Heterogeneity between studies</u>

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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.

45 The variety of combinations of further patient treatment and assessment related factors prevented meaningful 46 47 subgrouping of studies for additional sensitivity analyses, and the likeliness of their contribution to the observed 48 heterogeneity makes formal assessment for publication bias unadvisable.(64) However, some distinct observations 49 50 are worth to be discussed. Certain patient populations might be at higher risk to experience acupuncture related AE; 51 e.g. in one study conducted among CMD patients AE were prominently frequent.(35) The role of acupuncture regimens 52 in explaining heterogeneity could not be determined due to the limited information about number, location, and 53 54 stimulation of needles. In contrast, the number of treatments per acupuncture series and study type seemed not to 55 have impacted reported AE incidences. 56

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

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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 2 3 mechanisms and anti-inflammatory humoral responses through micro-trauma of skin and tissue, it can be argued that 4 moderate local reactions are indeed desired reactions indicating an induction of regulative processes. Mild pain and a 5 6 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 8 9 sensation along the channels) supposedly related to acupuncture effectiveness.(19) The loss of small drops of blood 10 upon needle withdrawal is interpreted as a sign for the patient's constitution called "excess" or "excess heat" in TCM 11 terminology and was suggested not to be interpreted as AE.(65) On the other hand, standard text books explicitly 12 13 explain needling techniques avoiding pain and bleeding. (20, 66) This debate calls for a uniform internationally 14 recognized consensus on the definition of local acupuncture reactions as AE e.g. according to their quality and 15 16 intensity. 17

18 In addition, included studies differed in reporters (acupuncturists, patients, acupuncturists also questioning patients, 19 and independent assessors), the type of documentation (selection list, open questions, or a combination of both), and 20 assessment time points. Due to the large variability of combinations the individual impact of these factors could not 21 22 be estimated, but literature suggests that patients report more AE than therapists, (67) and that open questions 23 presented to patients lead to lower risk estimates than the presentation of a selection list of possible AE.(29) Thus, 24 25 standardized AE assessment methods should be established for acupuncture studies. 26

27 Risk of bias in included studies 28

29 Although, large prospective studies are among the most important sources of safety data, they come with the known 30 risk for information, selection, and confounding bias.(68) Risk of information bias was mostly related to poor reporting 31 of acupuncture regimens and the discrepancies in AE definition and assessment. This is in line with the shortcoming 32 33 identified for reporting of AE in acupuncture randomized controlled trials.(69) Possible causes of selection bias 34 identified were mainly voluntary participation of practitioners, unsystematic patient selection, and study conductance 35 36 in highly specialized institutions. Practical reasons make these causes of selection bias inherent to safety studies. They, 37 however, are unlikely to importantly impair external validity, considering the large number of patients and treatments, 38 39 the variety of countries in which studies were conducted, and the inclusion of different study designs. Future large 40 scale comparative safety studies along with modern statistical methods for confounder adjustment could be used to 41 42 contrast AE risks related acupuncture to AE risks associated with other treatments and to identify patient and 43 treatment characteristics associated with AE in real world clinical settings.(70) 44

Limitations

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47 First, it is debatable whether studies should be summarized irrespective of whether AE not necessarily related to 48 acupuncture or adverse reactions likely caused by acupuncture were reported. In order to provide the most 49 50 comprehensive information possible respective sensitivity analyses were conducted. Additionally, the risk estimates 51 for the different types of minor adverse events are likely to be slightly overestimated and should be interpreted as a 52 rough indication that allows to distinguish frequent from less frequent acupuncture related minor AE. In categorizing 53 54 the minor AE it was disregarded that several different AE falling in one category could have occurred in the same 55 patient or during the same treatment. Also, calculations of risks in treatments with AE per total number of treatments 56 57 could not adjust for the fact that multiple AE assessments in the same patient are not independent. Furthermore, zero 58 incidences of certain types of AE were not available. Finally, the causality assessment presented for SAE is limited to 59 60

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.

Page	19 of 48 BMJ Open
1	Figure legends
2 3	Figure 1: Flow diagram
4	Designed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)(24)
5 6	Figure 2: Meta-analyses of the overall risk for acupuncture related adverse events
7 8 9 10	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.
11	Figure 3: Meta-analyses of the overall risk for serious adverse events related to acupuncture
12 13 14 15	Summary risk estimates for serious adverse events (SAE) were calculated as the number SAE cases relative to the tota number of patients or treatments, respectively.
16	Figure 4: Meta-analyses of the overall risk for adverse events (AE) requiring treatment
17 18 19 20	Summary risk estimates for AE requiring treatment were calculated as the number of patients with such AE relative to the total number of patients.
21 22	Figure 5: Risk of bias assessment
23 24 25 26 27 28 29 30 31 32 33 45 37 38 39 40 41 42 43 44 50 51 52 54 55 56 57 58	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 <u>www.icmje.org/coi_disclosure.pdf</u> 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 lecturing 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).

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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.

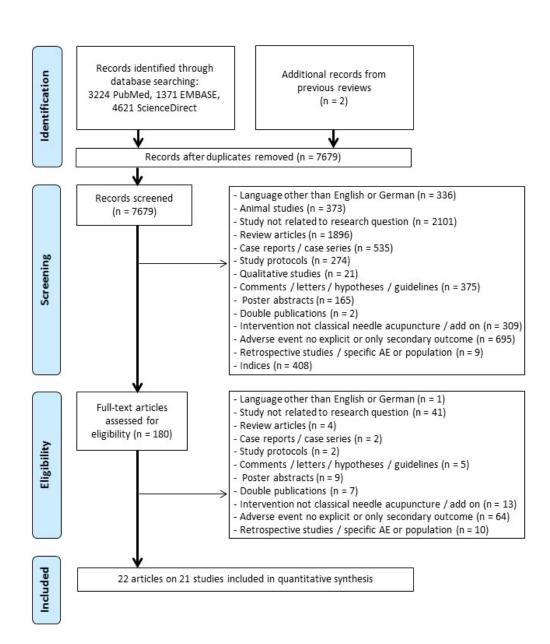
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Study	patients with AE	total patients	Risk p	er 10	0 patients	Events	9	5%-CI		Weight (random)
Chung 2015	25	59	1	_		42.37	[30.15; 5	55 091	0.0%	1.2%
Wen 2016	5		1				[1.34;			
Melchart 1998	34						[20.48: 3			
Leung 2009	6						[0.86;			
Ernst 2003	153						[32.79; 4			
Zhao 2011	74									
							[2.97;			
Weidenhammer 2008 pat.	560		Ť				[8.61; 1			
MacPherson 2004	682		1				[9.99;			
Melchart 2004	6942		1				[6.94;			
Witt 2009	19726		-				[8.49;			
Weidenhammer 2008 ther.	39078	503397	1			7.76	[7.69;	7.84]	59.5%	15.2%
Fixed effect model		845637	İ				[7.88;		100.0%	
Random effects model			•			9.31	[5.10; 1	4.62]		100.0%
Heterogeneity: $I^2 = 99\%$, $\tau^2 =$	= 0.0004, <i>p</i> < 0.01	0	10 20) 30	40 50	60				
Overall AE risk per acu	inuncture treati	-	10 20	50	40 50	60				
	reatments with AE		Risk	per 1	00 treatm	ents Eve	nts	95%		ght Wei ed) (rando
Melchart 1998	106				_		.83 [7.2			2% 19.
Leung 2009	8		*				.40 [0.			6% 19.
Ernst 2003	402	3535				11	.37 [10.3	35; 12	.44] 6.	4% 20.
da Silva 2014	1092	13884		÷.		7	.87 [7.	42; 8	.32] 25.	2% 20.
MacPherson 2001	5179	34407			+	15	.05 [14.6	58; 15	.43] 62.	5% 20.
Fixed effect model		55026			\$	11	.88 [11.6	1; 12.	15] 100.	0%
Random effects model				-		- 7	.57 [1.4	3; 17.	95]	100.
Heterogeneity: $I^2 = 100\%$, τ^2	= 0.0103, p < 0.01				1 1				-	
, , , , , , , , , , , , , , , , , , ,		() 5	;	10 15	20				
Overall risk for AE re	lated to acupur	ncture among pa	atients	unde	ergoing a	treatmer	t series		Mainh4	Mainha
Study	patients with AE	total patients	Risk p	er 100) patients	Events	95			Weight (random)
Wen 2016	5	120				4.17	[1.34;	8.451	0.0%	1.7%
Leung 2009	6	254 -		-		2.36	[0.86;	4.581	0.0%	3.2%
Weidenhammer 2008 pat.	560						[8.61; 1		0.7%	16.8%
MacPherson 2004	682	6348			_		[9.99; 1		0.8%	17.0%
Melchart 2004	6942	97733			*		[6.94;		11.6%	20.3%
Witt 2009	19726						[8.49;		27.2%	20.5%
Weidenhammer 2008 ther.		503397					[7.69;			20.5%
weidennammer 2000 ther.	39076	505587				1.10	[7.09;	1.04]	55.170	20.0%
Fixed effect model		843080			\$		[7.88; 4		100.0%	-
Random effects model				-		8.23	[6.42; 10	D.25]		100.0%
Heterogeneity: $I^2 = 98\%$, $\tau^2 =$	= 0.0002, <i>p</i> < 0.01	I		1	- I	I				
		0	2 4	6	8 10	12				

Overall risk for AE	related to acupunctu	re per treat	ment								Weight	We
Study	treatments with AE tota	al treatments	Ri	sk p	per 10	00 tre	atmo	ents	Events	95%-CI	(fixed)	(rand
Leung 2009	8	2000							0.40	[0.17; 0.72]	4.0%	3
da Silva 2014	1092	13884	H	e					7.87	[7.42; 8.32]	27.6%	3
MacPherson 2001	5179	34407			+				15.05	[14.68; 15.43]	68.4%	3
Fixed effect model		50291		0					11.99	[11.71; 12.28]	100.0%	
Random effects mode			-	-	-	_	_		6.08	[0.00; 38.76]		100

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Heterogeneity: $I^2 = 100\%$, $\tau^2 = 0.0133$, p < 0.01

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7	A Overall SAE risk among patien	ts undergoing an acupuncture series	Weight Weight
8	Study patient	s with SAE total patients Risk per 10000 p	
-	Wen 2016 Leung 2009	0 120	→ 0.00 [0.00; 79.82] 0.0% 0.4% → 0.00 [0.00; 37.76] 0.0% 0.8%
9	Yamashita 2000 da Silva 2014	0 391	→ 0.00 [0.00; 24.54] 0.0% 1.2%
10	Zhao 2011	0 1157	0.00 [0.00; 8.30] 0.1% 3.3% 0.00 [0.00; 4.88] 0.2% 5.1%
11	Furuse 2017 Yamashita 1999	0 2180 2 5008	0.00 [0.00; 4.40] 0.2% 5.5% 3.99 [0.38; 11.44] 0.4% 9.5%
12	MacPherson 2004 Melchart 2004	3 6348 6 97733	
13	Endres 2004 Weidenhammer 2008 ther.	45 190924 17 882847	2.36 [1.72; 3.10] 16.1% 21.1% 0.19 [0.11; 0.29] 74.3% 21.6%
14	Fixed effect model	1188930	0.43 [0.32; 0.56] 100.0%
15	Random effects model Heterogeneity: $I^2 = 88\%$, $\tau^2 < 0.0001$,	*	1.01 [0.23; 2.33] 100.0%
	Theterogeneity. 7 = 00 %, 1 < 0.0001,	0 2 4 6 8 1	0 12 14
16	B Overall SAE risk per acupunctu	the second se	Weight Weight
17			+06 treatments Events 95%-CI (fixed) (random)
18	Yamashita 2000 Wen 2016	0 1441 0 1680	→ 0.00 [0.00; 666.31] 0.0% 0.4% → 0.00 [0.00; 571.54] 0.0% 0.5%
19	Leung 2009 Park 2010	0 2000	→ 0.00 [0.00; 480.11] 0.0% 0.6% → 0.00 [0.00; 312.69] 0.0% 0.9%
20	da Silva 2014 Furuse 2017	0 13884 0 14039	0.00 [0.00; 69.17] 0.1% 3.5% 0.00 [0.00; 68.41] 0.1% 3.6%
21	MacPherson 2004	3 30196	> 99.35 [18.73; 243.56] 0.3% 6.3%
22	White 2001 MacPherson 2001	0 34407	0.00 [0.00; 30.18] 0.3% 6.5% 0.00 [0.00; 27.91] 0.3% 6.8%
	Zhao 2011 Yamashita 1999	0 39360 2 65482	0.00 [0.00; 24.40] 0.4% 7.4% 30.54 [2.88; 87.54] 0.6% 9.8%
23	Melchart 2004 Endres 2004	6 760000 45 1770000	7.89 [2.84; 15.48] 7.1% 17.2% 25.42 [18.54; 33.39] 16.5% 18.0%
24	Weidenhammer 2008 ther.	17 7945000 •	2.14 [1.24; 3.28] 74.2% 18.4%
25	Fixed effect model Random effects model	10712382	4.75 [3.53; 6.14] 100.0% 7.98 [1.39; 20.00] 100.0%
26	Heterogeneity: $l^2 = 85\%$, $\tau^2 < 0.0001$,	p < 0.01	
27	C Overall risk for SAE related to	acupuncture among patients underg	80 100 120 140
28		s with SAE total patients Risk per 10000	weight weight
	Wen 2016	0 120	→ 0.00 [0.00; 79.82] 0.0% 0.2%
29	Leung 2009 Yamashita 2000	0 254	→ 0.00 [0.00; 37.76] 0.0% 0.3% → 0.00 [0.00; 24.54] 0.0% 0.5%
30	da Silva 2014 Furuse 2017	0 1157	0.00 [0.00; 8.30] 0.1% 1.5% 0.00 [0.00; 4.40] 0.2% 2.7%
			4.73 [0.89; 11.58] 0.6% 7.2%
31	MacPherson 2004	3 6348	
31 32			0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3%
	MacPherson 2004 Melchart 2004 Weldenhammer 2008 ther. Fixed effect model	3 6348 6 97733 -	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0%
32 33	MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther.	3 6348 6 97733 17 882847 991030	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0%
32 33 34	MacPherson 2004 Melchart 2004 Weldenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: $r^2 = 41\%$, $\tau^2 < 0.0001$,	3 6348 97733 ↔ 17 882847 991030 ↔ p = 0.11 0 2 4 6 8 1	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0%
32 33 34 35	MacPherson 2004 Melchart 2004 Weldenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: / ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to	3 6348 6 97733 17 882847 991030 • • • • • • • • • • • • • • • • • •	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% 0 12 14 Weight Weight
32 33 34 35 36	MacPherson 2004 Melchart 2004 Welchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, <u>D Overall risk for SAE related to</u> Study treatme	p = 0.11 $0 2 4 6 8 7$ $2 4 6 8 7$ $2 4 6 8 7$ $2 4 6 8 7$ $2 4 6 8 7$ $2 5 6 7$ $2 5 6 7$ $3 7 7 8$ $5 7 7 7 7 8$ $5 7 7 7 7 8$ $5 7 7 7 7 8$ $5 7 7 7 7 7 8$ $5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% 10 12 14 +06 treatments Events 95%-CI (fixed) (random)
32 33 34 35 36 37	MacPherson 2004 Melchard 2004 Weldanhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, t ² < 0.0001, D Overall risk for SAE related to Study treatme Yamashita 2000 Wen 2016	p = 0.11 0 2 4 6 8 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% 10 12 14 +06 treatments Events 95%-CI (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3%
32 33 34 35 36	MacPherson 2004 Meichard 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: <i>t</i> ² < 0.0001, D Overall risk for SAE related t Study treatm Yamashita 2000 Wen 2016 Leung 2009 Park 2010	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% +06 treatments Events 95%-CI (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 571.54] 0.0% 0.3% → 0.00 [0.00; 371.54] 0.0% 0.4% → 0.00 [0.00; 312.69] 0.0% 0.4%
32 33 34 35 36 37	MacPherson 2004 Meichard 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: <i>I</i> ² = 41%, τ ² < 0.0001, D Overall risk for SAE related t r Study treatm Yamashita 2000 Wen 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017	3 6348 6 97733 17 882847 991030 <i>p</i> = 0.11 0 2 4 6 8 0 2 0 2 4 6 8 0 2 4 6 8 0 2 146 0 1680 0 1441 0 1680 0 3071 0 13884 0 1439	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% +06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 460.1] 0.0% 0.3% → 0.00 [0.00; 480.1] 0.0% 0.4% → 0.00 [0.00; 681.7] 0.2% 2.6%
32 33 34 35 36 37 38	MacPherson 2004 Melchart 2004 Welchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Wen 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.23 [0.15; 0.34] 100.0% 0.23 [0.15; 0.34] 100.0% 0 12 14 ★06 treatments Events 95%-CI (fixed) (random) → 0.00 [0.00; 68.51] 0.0% 0.3% → 0.00 [0.00; 751.54] 0.0% 0.3% → 0.00 [0.00; 751.54] 0.0% 0.3% → 0.00 [0.00; 751.54] 0.0% 0.3% → 0.00 [0.00; 68.17] 0.0% 0.6% → 0.00 [0.00; 68.17] 0.2% 2.6% → 99.35 [18.73; 243.56] 0.3% 5.4%
32 33 34 35 36 37 38 39 40	MacPherson 2004 Meichard 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: <i>I</i> ² = 41%, τ ² < 0.0001, D Overall risk for SAE related t r Study treatm Yamashita 2000 Wen 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0.61 [0.22; 1.20] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] - 100.0% 10 12 14 +06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 65.15] 0.0% 0.3% → 0.00 [0.00; 65.17] 0.2% 0.3% → 0.00 [0.00; 68.17] 0.2% 0.6% → 0.00 [0.00; 68.41] 0.2% 2.6% → 99.35 [18.73; 243.56] 0.3% 5.4%
32 33 34 35 36 37 38 39 40 41	MacPherson 2004 Meichard 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: <i>t²</i> = 41%, τ ² < 0.0001, D Overall risk for SAE related tr Study treatme Yamashita 2000 Wen 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Meichart 2004 Weidenhammer 2008 ther.	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% - 0.45 [0.06; 1.18] - 100.0% 10 12 14 +06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 681.11] 0.0% 0.4% → 0.00 [0.00; 312.69] 0.0% 0.6% → 0.00 [0.00; 684.11] 0.2% 2.6% → 99.35 [18.73; 243.56] 0.3% 5.4% 7.89 [2.84; 154.8] 8.7% 38.2% 2.14 [1.24; 3.28] 90.6% 49.5%
32 33 34 35 36 37 38 39 40 41 42	MacPherson 2004 Meichard 2004 Veidenhammer 2008 ther. Fixed effect model Random effects model Heterogeneity: / ² < 0.0001, D Overall risk for SAE related tr Study treatmer Yamashita 2000 Wen 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Meichard 2004 Weidenhammer 2008 ther.	$\begin{array}{c} 3 & 6348 \\ 6 & 97733 \\ 17 & 882847 \\ 991030 \\ p = 0.11 \\ 0 & 2 & 4 & 6 & 8 \\ \hline \begin{array}{c} 0 \\ 2 \\ 0 \\ 1 \\ 0 \\ 0$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% 10 12 14 +06 treatments Events 95%-CI (fixed) (random) → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.4% → 0.00 [0.00; 681.1] 0.0% 0.4% → 0.00 [0.00; 681.4] 0.0% 0.4% → 0.00 [0.00; 681.4] 0.0% 54% → 7.89 [2.84; 15.48] 8.7% 38.2% ↓ 2.57 [1.62; 3.74] 100.0% 5.45 [0.50; 15.67] 100.0%
32 33 34 35 36 37 38 39 40 41 42 43	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	$\begin{array}{c} 3 & 6348 \\ 6 & 97733 \\ 17 & 882847 \\ 991030 \\ p = 0.11 \\ 0 & 2 & 4 & 6 & 8 \\ \hline \begin{array}{c} 0 \\ 2 \\ 0 \\ 1 \\ 0 \\ 0$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% - 0.45 [0.06; 1.18] - 100.0% 10 12 14 +06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 681.11] 0.0% 0.4% → 0.00 [0.00; 312.69] 0.0% 0.6% → 0.00 [0.00; 684.11] 0.2% 2.6% → 99.35 [18.73; 243.56] 0.3% 5.4% 7.89 [2.84; 154.8] 8.7% 38.2% 2.14 [1.24; 3.28] 90.6% 49.5%
32 33 34 35 36 37 38 39 40 41 42 43 44	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	$\begin{array}{c} 3 & 6348 \\ 6 & 97733 \\ 17 & 882847 \\ 991030 \\ p = 0.11 \\ 0 & 2 & 4 & 6 & 8 \\ \hline \begin{array}{c} 0 \\ 2 \\ 0 \\ 1 \\ 0 \\ 0$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% 10 12 14 +06 treatments Events 95%-CI (fixed) (random) → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.4% → 0.00 [0.00; 681.1] 0.0% 0.4% → 0.00 [0.00; 681.4] 0.0% 0.4% → 0.00 [0.00; 681.4] 0.0% 54% → 7.89 [2.84; 15.48] 8.7% 38.2% ↓ 2.57 [1.62; 3.74] 100.0% 5.45 [0.50; 15.67] 100.0%
32 33 34 35 36 37 38 39 40 41 42 43	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	$\begin{array}{c} 3 & 6348 \\ 6 & 97733 \\ 17 & 882847 \\ 991030 \\ p = 0.11 \\ 0 & 2 & 4 & 6 & 8 \\ \hline \begin{array}{c} 0 \\ 2 \\ 0 \\ 1 \\ 0 \\ 0$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% 10 12 14 +06 treatments Events 95%-CI (fixed) (random) → 0.00 [0.00; 671.54] 0.0% 0.3% → 0.00 [0.00; 671.54] 0.0% 0.4% → 0.00 [0.00; 681.1] 0.0% 0.4% → 0.00 [0.00; 681.4] 0.0% 0.4% → 0.00 [0.00; 681.4] 0.0% 54% → 7.89 [2.84; 15.48] 8.7% 38.2% ↓ 2.57 [1.62; 3.74] 100.0% 5.45 [0.50; 15.67] 100.0%
32 33 34 35 36 37 38 39 40 41 42 43 44	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	p = 0.09 $p = 0.09$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 144 1$ $0 1680$ $0 2000$ 1441 $0 1680$ $0 3071$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 2000$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% *06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 684.1] 0.2% 2.6% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0%
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	$\begin{array}{c} 3 & 6348 \\ 6 & 97733 \\ 17 & 882847 \\ 991030 \\ p = 0.11 \\ 0 & 2 & 4 & 6 & 8 \\ \hline \begin{array}{c} 0 \\ 2 \\ 0 \\ 1 \\ 0 \\ 0$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% *06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 684.1] 0.2% 2.6% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0%
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	p = 0.09 $p = 0.09$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 144 1$ $0 1680$ $0 2000$ 1441 $0 1680$ $0 3071$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 2000$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% *06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 684.1] 0.2% 2.6% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0%
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	p = 0.09 $p = 0.09$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 144 1$ $0 1680$ $0 2000$ 1441 $0 1680$ $0 3071$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 2000$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% *06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 684.1] 0.2% 2.6% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0%
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	p = 0.09 $p = 0.09$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 144 1$ $0 1680$ $0 2000$ 1441 $0 1680$ $0 3071$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 2000$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% *06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 684.1] 0.2% 2.6% → 0.00 [1.00; 69.17] 0.2% 2.6% → 0.00 [1.00; 69.17] 0.2% 2.6% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0%
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	MacPherson 2004 Melchart 2004 Welchart 2008 ther. Fixed effect model Random effects model Heterogeneity: I ² = 41%, τ ² < 0.0001, D Overall risk for SAE related to Study treatm Yamashita 2000 Ven 2016 Leung 2009 Park 2010 da Silva 2014 Furuse 2017 MacPherson 2004 Melchart 2004 Weidenhammer 2008 ther. Fixed effect model Random effects model	p = 0.09 $p = 0.09$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 4 6 8 7$ $0 2 144 1$ $0 1680$ $0 2000$ 1441 $0 1680$ $0 3071$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 13884$ $0 2000$	0.61 [0.22; 120] 9.9% 37.3% 0.19 [0.11; 0.29] 89.1% 50.3% 0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] 100.0% *06 treatments Events 95%-Cl (fixed) (random) → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 666.31] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.3% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 686.1] 0.0% 0.4% → 0.00 [0.00; 684.1] 0.2% 2.6% → 0.00 [1.00; 69.17] 0.2% 2.6% → 0.00 [1.00; 69.17] 0.2% 2.6% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0% → 0.00 [0.00; 684.1] 0.0% → 0.0%
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Study	requiring treatmen	t total patients	Risk per 1000 pa	tionto	Events	95% CI	Weight (fixed) (I	Weight
Chung 2015	requiring treatmen		Risk per 1000 pa	uents		0.01; 65.17]	0.0%	8.8%
Wen 2016 Leung 2009) 120 -			0.00	[0.00; 7.98] [0.00; 3.78]	0.0%	10.8% 12.3%
Yamashita 2000 da Silva 2014) 391 🕂	-		0.00	[0.00; 2.45] [0.00; 0.83]	0.0%	12.8% 13.5%
Melchart 2004 Witt 2009	4963	97733 =		-	0.06	[0.02; 0.12] 21.06; 22.25]	8.1% 18.9%	13.9% 13.9%
Weidenhammer 2008 acupuncturists						[0.01; 0.03]	72.9%	13.9%
Fixed effect model Random effects model		1211791			1.01 1.14	[0.95; 1.07] [0.00; 7.37]	100.0%	 100.0%
Random effects model Heterogeneity: $l^2 = 100\%$, $\tau^2 = 0.0073$, μ	p = 0	0	5 10 15	5 20				
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	 Study design and objectives 				Ŀ	U	U	U	ſ	C	C	€	Ŀ	U		(
11	Bias in selection of subjects & constitution of study groups	H U	U	U	U	H	H	U	U	U	U	U	U	U	U	
	 Bias due to withdrawals or loss of follow-up 	()	U	U	U	U		U	C	L	U	U	U	L		(
	D. Information bias regarding the	UU	U	U	U	U	H	U	U	U	U	U	U	U	U	(
14	drug safety outcome E. Other information bias		U	U	U	U	Ā	Ā	 C /ul>	U	U		U	U	U	1
15	F. Statistical methods to control															Ċ
16	confounding G. Statistical methods excluding															
17	those to control confounding				•	•	•	•		•	•			•	•	
18	H. Conflict of interest			U	U	U	U	U	H	H	U	C	H	J	H	
19	Summary risk of bias assessment	U U	U	U	U	U	U	U	U	U	U	U	U	U	U	
20																
21	B. Bias in selction of subects &	. Study design														
22	C. Bias due to wit	hdrawals or l	oss of fol	llow-up	-								-			
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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

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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.**

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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, University 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

Granten funder of award number and the date of award

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

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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.

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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 metaanalysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used. **BMJ** Open

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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) me No	ta-analysis
Intervention No	
Meta-analysis No	
Methodology No	
Narrative synthesis No	
Network meta-analysis No	
Pre-clinical No	
Prevention No	
Prognostic No	
Prospective meta-analysis (PM/ No	Α)
Review of reviews	

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1	PROSPERO	Nation
1 2	International prospective register of systematic reviews	He
3 4	No	
5 6 7	Service delivery No	
8 9	Synthesis of qualitative studies No	
10 11 12	Systematic review Yes	
13 14 15	Other No	
16 17 18 19 20	Health area of the review Alcohol/substance misuse/abuse No	
21 22 23	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	
24 25	Cancer No	
26 27	Cardiovascular No	
28 29	Care of the elderly No	
30 31 32	Child health No	
33 34	Complementary therapies Yes	
35 36	COVID-19 No	
37 38 39	Crime and justice	
40 41	Dental No	
42 43	Dental No Digestive system No Ear, nose and throat	
44 45 46	Ear, nose and throat No	
47 48	Education No	
49 50	Endocrine and metabolic disorders No	
51 52 53	Eye disorders No	
54 55	General interest No	
56 57	Genetics No	
58 59 60	Health inequalities/health equity No	

NHS National Institute for Health Research

International	nrospective	rogistor of	svstematic reviews	
IIILEIIIALIUIIAI	DIOSDECLIVE	reuister or	Systematic reviews	

PROSPERO

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2	International prospective register of systematic reviews
3	Infections and infestations
4	No
5	International development
6	No
7	Mental health and behavioural conditions
8 9	No
, 10	
11	Musculoskeletal No
12	
13	Neurological
14	No
15	Nursing
16	No
17	Obstetrics and gynaecology
18 19	No
20	Oral health
20	No
22	Palliative care
23	No
24	Perioperative care
25	No
26	Physiotherapy
27	No
28 29	No Oral health No Palliative care No Perioperative care No Physiotherapy No Pregnancy and childbirth
29 30	No
31	
32	Public health (including social determinants of health)
33	
34	Rehabilitation No
35	
36	Respiratory disorders
37 38	No
30 39	Service delivery
40	No
41	Skin disorders
42	No
43	Social care
44	No
45	Surgery
46 47	No
47 48	Tropical Medicine
49	No
50	Urological
51	No
52	Wounds, injuries and accidents
53	No
54	Violence and abuse
55	No
56 57	
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31. Language.

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

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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

PROSPERO International prospective register of systematic reviews

NHS National Institute for Health Research

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.

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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

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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

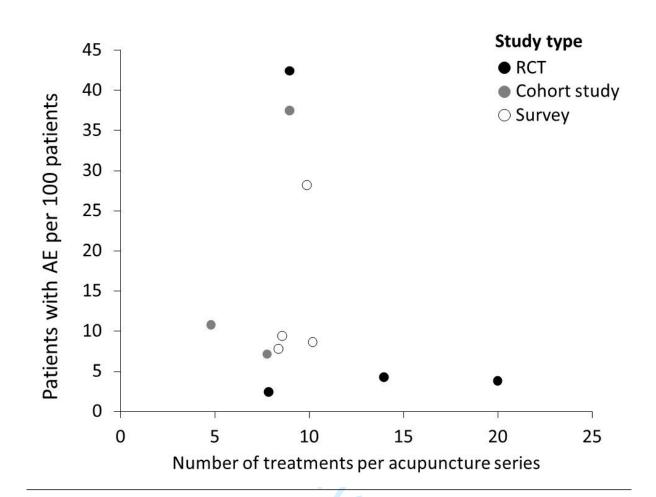
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For pertraviewindther://bm/inpenpini-com/site/about/opugelines.xhtml

1	Bleeding		
2	• Bleeding	 Small hemorrhage 	• Ecchymosis or hematoma
3	 Bleeding at needling site 	 Lesion of blood vessel 	accompanied by pain
4	 Mild / transient / minor bleeding 	Bruising	 Ecchymosis or hematoma without
5	 Subcutaneous bleeding 	 Bruising at needling site 	pain
6	Hematoma	 Mild / transient bruising 	 Petechia or ecchymosis
7	 Minor hematoma 	 Heavy bruising 	
8	 Subcutaneous / superficial hematoma 	 Subcutaneous bruise 	
9	Local pain		
10	• Pain	 Pain upon insertion / stimulation 	 Mild pain at the acupuncture site
11	 Needle (-site) pain 	 Pain while needle was in place 	more than one hour after treatment
12	 Pain where needle was inserted / at 	 Pain upon needle withdrawal at the 	 Pain disappearing after > 3 days
13	the site of the needle / in the	acupuncture point	 Chest pain (pneumothorax ruled out)
14	punctured region	 Pain after needle was removed 	 Electroacupuncture problems e.g. too
15	 Mild / transient pain at needling site 	 Remaining / residual needle site pain 	strong current resulting in pain
	 Severe / strong / significant pain at 	 Prolonged / unacceptable pain at 	 Local muscle pain
16 17	needling site	needle site	 Unknown pain
17	Other local AE		
18	• Wheal	 Inflammation at application site 	• Significant rash on abdomen few days
19	• (Local) swelling	• Itch	after acupuncture
20	• Redness	Itching and redness	Cellulitis after treatment of
21	• Flare	 Itching in the punctured region 	edematous leg
22	Localized erythema	Itching and erythema (suspected	Edema in m. tibialis with anterior toe
23	Needle-site / local skin reaction	contact dermatitis)	lifting weakness (fully resolved)
24	 (Skin) irritation at acupuncture point 	Local allergic reaction (uticaria)	Other local AE (around the
25	Skin infection	Needle allergy	acupuncture site)
26	 Local (skin) infection 	 Allergic phenomena / reaction 	
27	Central nervous system		
28	• Aphasia	• Vertigo	Disturbed vision
29	• Dizziness	• Disorientation (length unspecified, 1	Spontaneous sensory perceptions
30	Mild / transient dizziness	h, 1 day)	• Shivering
31	• Imbalance	Severe disorientation	Seizure shortly after treatment
32	Severe dizziness, vertigo or loss of	Disturbed speech	• Tremor
33	balance	Slurred speech	
34	Peripheral nervous system		
35	Cold sensation at needling site	Prolonged deqi	Hypaesthesia with numbness for
36	 Feeling of acupuncture point at 	Strong acupuncture or heavy	three days
37	contralateral arm • Paraesthesia	sensation	Insensibility Itabiag ains & peoples tingling or
38		Hypaesthesia	 Itching, pins & needles, tingling or huming constition
39	Temporary paraesthesia Tigeling	Numbness	burning sensation
40	Tingling Tingling Tingling	Numbness in upper extremity	Nerve irritation
	 Tingling, prickling, burning, dysosthosia 	Numbness and unusual sensation	• Neuritis
41 42	dysesthesia	Severe stiffness or numbness	
42 42	Aggravation of symptoms	• Transient aggravation of symptoms	• Worsoning of condition (ofter
43	 Aggravation Aggravation of complaints / existing 	 Transient aggravation of symptoms Aggravation of existing symptoms 	 Worsening of condition (after removing needles)
44 45	 Aggravation of complaints / existing ailment / existing symptoms 	 Aggravation of existing symptoms followed by improvement 	Headache and or facial pain
45	 Unexpected, severe or prolonged 	 Deterioration / exacerbation of 	 pressure and or tension in the teeth
46	worsening of symptoms	symptoms	 Increased pain
47	 Aggravation of symptoms during 	 General aggravation of symptoms 	- marcasca pam
48	acupuncture session / after treatment	Worsening of health state	
49	Vegetative nervous system		
50	• (Generalized) sweating	Abnormal tiredness	• Significant / severe drowsiness
51	 Isolated sweating of hands 	 Severe / significant tiredness or 	 Drowsiness not causing hazard
52	 Mild sweating 	exhaustion	 Prolonged drowsiness (one day, one
53	 Flushed cheeks and body warmth 	Lethargy	week)
54	Hot flash	• Dazed	Drowsiness or restlessness
55	 Feeling of warm / heat / cold 	 Vasovagal reaction: collapse, 	Orthostatic problems
56	Coldness / feeling cold	dizziness, nausea & vomiting	Malaise
57	Freezing	Unconsciousness	Poor concentration
58	 (Feeling of) fatigue 	Fainting	• Dry lips / mouth
59	Extreme feeling of fatigue	 Faint / dizzy 	Xerostomia
60	 Feeling tired (mild transient) 	Feel faint / drowsy	Hunger / thirst
	 Tiredness and exhaustion 	 Feel faint (significant) 	
		. cer fante (Significante)	

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 	 Mild transient pain not at 	 Generalized muscle pain
at needling site	needling site	 Other / unspecified pain / aches
 Reactive pain at other body sites 	 Chest pain / tightness 	
Gastrointestinal / gynaecological system		
Nausea	 Tiredness next day after ten hours of 	 Increased peristalsis
 Mild and transient nausea 	diarrhoea (significant)	 Loss of appetite
Severe nausea	 Stomach ache 	 Other gastrointestinal complaints
Vomiting	 Abdominal distension 	 Increased haemorrhage during
 Severe vomiting 	 Impaired bowel function 	menses
 Constipation 	 Digestive problems 	 Menstrual problems
Diarrhoea	 Entero- / gastrospasm 	
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	č
Emotional interference		
Aggressive behaviour	Depressive mood	 Severe emotional outburst and angoing
Anxiety	• Discomfort	at practitioner
 Anxiety and panic (up to one hour) 	Restlessness or nervousness	• Fear
 Significant panic with sensation of 	 Disorientation, anxiety, nervousness, 	 Grief / crying / tearful
heat and sweatiness	insomnia or emotional	Needle phobia, anxiety and rage
 Severe panic / agitation / depression 	 Emotional /psychological reaction 	• (Severe) nightmares
with anxiety	• (Uncontrolled) euphoria	Other mood swings
 Depressed emotional state or 	• Significant emotional release (manic,	-
neurovegetative dystonia	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	• Failure to remove needle(s)	
treatment room for too long	Forgotten / dropped needle	
Broken needle	Needle lost or forgotten	
 Stuck or bent needle 	5	
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)
• Fever	 Concomitant diseases of recent 	adverse events
Angina	appearance	 other negative reactions
Eye irritation	Change of taste	Unknown due to incomplete record
	Change of weight / weight reduction	form

n 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

Page	46	of	48
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Study	Total number of patients	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]			44.76	2.04	0 77				
Yamashita 2000	391	25.18	0.26 [0.00; 1.00] 8.07	1.02 [0.27; 2.26] 0.24	11.76 [8.76; 15.14] 6.36	2.81 [1.41; 4.68] 0.98	0.77 [0.15; 1.87] 6.11	4.89		1.96	17.85
Ernst 2003	409	[21.10; 29.50] 3.40	8.07 [5.63; 10.90] 0.05	[0.00; 0.96]	[4.20; 8.92] 0.10	[0.26; 2.16]	[4.00; 8.64] 0.05	4.89 [3.01; 7.19]		[0.84; 3.52] 0.05	[14.29; 21.70]
Zhao 2011	1968	[2.65; 4.25] 12.80	[0.00; 0.20] 6.24		[0.01; 0.29]	1.06	[0.00; 0.20]			[0.00; 0.20]	1.10
Furuse 2017	2180	[11.43; 14.23]	[5.26; 7.29]			[0.67; 1.53]					[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]	0.35	0.08 [0.07; 0.10]	0.76	0.22	0.07 [0.05; 0.08]
Witt 2009 Weidenhammer	229230	6.15 [6.05; 6.24] 4.84	0.45 [0.43; 0.48] 3.95	0.60 [0.57; 0.63] 0.15	0.30 [0.28; 0.33] 0.08	0.40 [0.38; 0.43] 0.08	0.26 [0.24; 0.28]	0.26 [0.24; 0.28]	0.76 [0.72; 0.79]	0.22 [0.20; 0.24] 0.01	0.11 [0.10; 0.12] 0.26
2008 therap.	503397	[4.78; 4.90]	[3.90; 4.01]	[0.14; 0.16]	[0.07; 0.08]	[0.07; 0.09]	0.20	0.10	0.74	[0.01; 0.02]	[0.25; 0.28]
Fixed effect		5.09 [5.05; 5.13] 4.67	1.81 [1.78; 1.84] 3.75	1.85 [1.83; 1.88] 2.79	0.25 [0.24; 0.26] 1.95	0.29 [0.28; 0.30] 1.48	0.28 [0.26; 0.31] 1.45	0.18 [0.17; 0.19] 0.69	0.74 [0.71; 0.77] 0.60	0.06 [0.05; 0.06] 0.60	0.19 [0.18; 0.20] 0.57
Random effect		[2.08; 8.22]	[0.74; 8.94]	[0.02; 10.01]	[0.40; 4.63]	[0.00; 5.90]	[0.07; 4.51]	[0.02; 2.34]	[0.21; 1.20]	[0.04; 1.81]	[0.01; 1.95]
tau²		0.0008	0.0085	0.0494	0.0012	0.0017	0.0018	0.0004	0.0005	0.0008	0.0003
l 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

Page 47 of 48

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	Total number				Risk as patients	ents with AE per 100 patients [95%-CI]				
itudy	of patients	Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
ist 1992	29			41,38				20,69		
	23	10.55		[24,41; 59,48]	4.60	0.00		[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]				
		[0.0980, 23.38]			[0,00, 0,52]	[0,00, 1,02]				
Ven 2016	120									
Aelchart 1998	121		0.83				0,83			
vieichait 1998	121		[0.00; 3.21]				[0,00; 3,21]			
eung 2009	254									
		0.51								
'amashita 2000	391	[0.0485; 1.46]								
rnst 2003	409	0.49	0.49	0,24			0,98			0,24
inst 2003	409	[0.0463; 1.40]	[0.05; 1.40]	[0,00; 0,96]			[0,26; 2,16]			[0,00; 0,96]
hao 2011	1968			0,10						
		0.05		[0,01; 0,29]		0.60			0.06	
uruse 2017	2180	0.05 [0.0000; 0.18]				0,60 [0,32; 0,96]			0,96 [0,60; 1,42]	
Veidenhammer		1.37	0.60	0,35		[0,52, 0,50]		0,13	[0,00, 1,72]	0,07
2008 pat.	5998	[1.0889; 1.68]	[0.42; 0.81]	[0,22; 0,52]				[0,06; 0,24]		[0,02; 0,15]
MacPherson	6348	1.21	-	-		1,04	1,24	0,74	0,44	5
2004	0540	[0.9585; 1.50]				[0,81; 1,30]	[0,99; 1,53]	[0,54; 0,97]	[0,29; 0,62]	
Aelchart 2004	97733	0.04				0,25				
		[0.0275; 0.05]				[0,22; 0,28] 0,00	0,04	0,04	0,00	
ndres 2004	190924					[0,00; 0,00]	[0,03; 0,05]	0,04 [0,03; 0,05]	[0,00; 0,00]	
	222222	0.52	0.27	0,08	0,09	0,01	0,09	0,04	0,01	0,02
Vitt 2009	229230	[0.4944; 0.55]	[0.25; 0.29]	[0,07; 0,09]	[0,08; 0,10]	[0,00; 0,01]	[0,08; 0,11]	[0,03; 0,05]	[0,00; 0,01]	[0,01; 0,02]
Veidenhammer	503397	0.03	0.42			0,28	, 0,0197			
008 therap.	505557	[0.0287; 0.04]	[0.40; 0.43]			[0,27; 0,30]	[0,02; 0,02]			
ixed effect		0.12		0,09	0,09	0,11	0,04	0,05	0,00	0,02
		[0.11; 0.13]	0.40	[0,08; 0,10]	[0,08; 0,10]	[0,11; 0,12]	[0,04; 0,04]	[0,04; 0,05]	[0,00; 0,01]	[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]
au²		0.0012	0.0001	0.0011	0.0029	0.0009	0.0002	0.0001	0.0002	0.0001
2		99.6%	96.4%	94.6%	= 58.2%	99.7%	98.7%	97.1%	98.3%	69.0%
		[99.6%; 99.7%]	[93.9%; 97.9%]	[90.2%; 97.1%]	[0.0%; 90.1%]	[99.7%; 99.8%]	[98.2%; 99.1%]	[95.3%; 98.2%]	[97.3%; 99.0%]	[0.0%; 91.0%]
-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

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Study	Total number of treatments	Bleeding	Pain	Other local AE	Vegetative nervous system	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal /gynaecologcial AE	Unclassifie 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]	[13.32, 17.08] 3.02 [2.74; 3.31]	[0.48, 1.40] 0.43 [0.33; 0.55]	[3.09, 3.87] 0.02 [0.00; 0.05]	[0.03, 1.72]	0.01 [0.00; 0.03]	0.11 [0.06; 0.17]	[0.00, 0.27]	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 Euruso 2017	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; 0.2
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; 6.2
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; 0.1
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; 0.0
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; 0.9
Leung 2009	2000	0.40 [0.17; 0.72]	0.40	0.40			0.00	0.05		0.00	0.00
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; 0.1
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]		0.00 [0.00; 0.01]	0.54	0.02 [0.01; 0.04]	0.46 [0.39; 0.5
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; 0.9
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; 0.2
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; 1.4
tau²		0.0169	0.0095	0.0004	0.0213	0.0055	0.0011	0.0008	0.0085	0.0008	0.0025
l 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

Page 49 of 48

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44 45 46

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Study Total number of treatments			Cardiovascular		Generalized	Needling	Emotional	Sleeping	Moxibustion	Respiratory
		Headache	system	Motor system	skin reaction	malpractice	interference	problems	AE	system
'amashita2000	1441	0.14 [0.01; 0.40]				0.62 [0.28; 1.10]				
laSilva2014	13884					0.24 [0.16; 0.33]				
lelchart1998	1200		0.08 [0.00; 0.33]				0.08 [0.00; 0.33]			
1acPherson 2005	9408						0.67 [0.51; 0.84]			
uruse2017	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]	
rnst2003	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]		0.01	
amashita 1999	65482					0.04 [0.03; 0.06]	0.01 [0.00; 0.02]		0.01 [0.00; 0.02]	
Park2009	1095									
eung2009	2000									
Park2010	3071	0.03 [0.00; 0.13]		0.10 [0.02; 0.24]		0.10 [0.02; 0.24]				
Vhite2001	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]	
AacPherson2001	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]	
ixed 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]	
andom 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]
au²		0.0002	0.0001	0.0001		0.0002	0.0004		0.0001	
2		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%]	
-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

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

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<u>Word count</u>

- 6404
- 51 52 53 54 55 56 57
- 57 58 59
- 60

Page	of 51 BMJ Open
1	Abstract
2 3	<u>Objective</u>
4 5	Overview on risks for acupuncture related adverse events (AE).
6	Design
7 8 9	Systematic review and meta-analysis of prospective studies.
9 10	Data sources
11 12	Pubmed, Scopus, and EMBASE from inception date to September 15, 2019.
13 14	Eligibility criteria for selecting studies
15 16 17	Prospective studies assessing AE caused by needle acupuncture in humans as primary outcome published in Englis or German
18 19	Data extraction and synthesis
20	Two independent researchers selected articles, extracted the data and assessed study quality. Overall risks and risk
21 22	for different AE categories were obtained from random effects meta-analyses.
23 24	Main outcomes
25 26	Overall risk for minor AE and serious AE (SAE) per patients and per treatments
27 28	<u>Results</u>
29	Out of 7679 screened articles 22 reporting on 21 studies were included. Meta-analyses suggest at least one A
30 31	occurring in 9.31% (95%-Cl 5.10 to 14.62; 11 studies) of patients undergoing an acupuncture series and in 7.57% (95%
32	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
33 34	per 10,000 patients and 7.98 (95%-Cl 1.39 to 20.00; 14 studies) per 1 million treatments, for AE requiring treatmer
54 35	1.14 (95%-Cl 0.00 to 7.37; eight studies) per 1000 patients. Heterogeneity was substantial (I²>80%). On average 9.4 A
36	occurred in 100 treatments of which half were bleeding, pain, or flare at the needle site argued to represent intende
37 38	acupuncture reaction. AE definitions and assessments varied largely.
39 40	
40 41	Acupuncture can be considered among the safer treatments in medicine. SAE are rare, and most common minor A
42 43	are very mild. AE requiring medical management are uncommon, but necessitate medical competence to assur
45 44	patient safety. Clinical and methodological heterogeneity call for standardized AE assessments tools, clear criteria fo
45	differentiating acupuncture related AE from therapeutically desired reactions, and identification of patient related ris
46 47	factors for AE.
48 49	PROSPERO registration number
50 51	CRD42020151930
52 53	
55 54	
55	Keywords
56 57	Adverse effects, adverse reactions, meta-analysis, safety, risk, pneumothorax
58	
59 60	

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

2 Acupuncture describes the insertion of fine needles at defined points on the patients' body for therapeutic or 3 preventive purposes. It is used worldwide with growing popularity. In the EU acupuncture was identified as the most 4 5 frequently provided method of complementary and alternative medicine (CAM) with 80,000 physicians and 16,380 6 non-medical practitioners.(1) In the UK alone 2.3 million traditional acupuncture treatments are carried each year.(2) 7 In the US the number of acupuncturists doubled between 2002 and 2012.(3) The effectiveness of acupuncture is 8 9 supported by level 1a evidence e.g. for chronic musculoskeletal pain and headache, (4-6) post-operative pain, (7, 8) 10 post-operative nausea and vomiting,(9) as well as allergic rhinitis.(10) Furthermore, promising evidence exists for its 11 12 potential role in the treatment of a large number of additional indications such as stroke rehabilitation,(11) 13 depression,(12) aromatase inhibitor induced arthralgia,(13) and asthma.(14) Thus, acupuncture offers a non-14 15 pharmacological treatment option for various highly prevalent conditions with great disease burden and significant 16 health economic impact. Long-term pharmacological treatment of these conditions is often associated with substantial 17 18 side effects.(15, 16) Consequently, also risk estimates on acupuncture related adverse events (AE) are required for 19 evidence-based risk benefit considerations that are essential for clinical decision making. 20

21 However, uncertainty remains about acupuncture safety. AE related to acupuncture are repeatedly and controversially 22 discussed both in scientific literature as well as in public media. An overview of systematic reviews in 2017 (17) 23 24 illustrates that many of the previous reviews on the safety of acupuncture just summarized case reports or case series. 25 In turn, those reviews including studies that do allow for AE frequency estimation, such as cohort studies and large 26 27 RCTs, mostly only addressed certain types of AE, particular patient groups, restricted acupuncture regimens, or certain 28 countries. These data are surely important for clinical decision making in particular cases, but leave the overall risk of 29 30 acupuncture related AE in the general population obscure. Additionally, debate exists about differentiating AE from 31 therapeutically intended reactions that are claimed to form part of the acupuncture treatment. For example, 32 33 international consensus exists that aggravation of symptoms represents an AE, since disease burden increases, 34 although transient worsening of symptoms followed by long-term improvements can be interpreted as a so called 35 healing crisis in complementary and alternative medicine.(18) In contrast, such consensus is still missing for local 36 37 reactions such as small bleedings upon needle withdrawal, needling pain, and flare around the needling site. These 38 are also referred to as beneficial signs by acupuncture experts and in standard text books and have been linked to 39 40 neurophysiological mechanisms of acupuncture, suggesting that quality and intensity of these events should be 41 considered when classifying them as AE.(19-21) 42

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

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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

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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

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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 10 11 related AE.(17) "Acupuncture" and "adverse effects" are MeSH terms. 12

13 In- and exclusion criteria 14

We included articles reporting on prospective studies (cohort studies, RCTs, surveys or surveillances) assessing AE 15 16 associated with needle acupuncture involving manual or electrical stimulation combined with or without moxibustion 17 in humans as their primary outcome. Case reports and case series were not included. Only articles published in English 18 19 or German were included. Publications on assessments of acupuncture point injection therapies or non-penetrating 20 acupuncture point stimulation such as laser acupuncture, acupressure or transcutaneous electrical nerve stimulation 21 22 (TENS) were excluded. We also excluded articles reporting solely on moxibustion or restricted acupuncture regimens 23 such as press-needle, auricular or one-point acupuncture. Trials focusing just on one type of acupuncture related AE 24 25 or just on a narrowly defined patient population were excluded. 26

27 Article selection and data extraction

28 Article selection was performed independently by two reviewers (WZ and PB, TS and PB, or LM and PB). Retrieved 29 30 records were first screened for eligibility by abstract. Full texts were obtained for the remaining articles. Final decision 31 about eligibility was obtained by consensus of all four reviewers. 32

33 Estimates of overall risks and risks for each reported type of AE were extracted as absolute number of patients with 34 AE per total number of patients and treatments with AE per total number of treatments. Data concerning AE from 35 36 sham- or placebo-acupuncture treatments were not extracted. The different types of AE were assigned to one of the 37 following categories: bleeding, local pain, other local AE, distant pain, central nervous system, peripheral nervous 38 39 system, vegetative nervous system, motor system, gastrointestinal / gynaecological system, cardiovascular system, 40 respiratory system, generalized skin reactions, headache, emotional interference, sleeping problems, AE related to 41 42 moxibustion, needling malpractice, aggravation of symptoms, other or unclassified AE (online supplementary 43 appendix S3). 44

45 Following the differentiation between AE and adverse drug reactions (ADR) defined by the International Conference 46 on Harmonization (ICH) of Good Clinical Practice, (26) articles were classified into reports on adverse events 47 48 irrespective of their causal relationship to acupuncture and adverse reactions for which a causal relationship was a 49 reasonable possibility. Serious adverse events (SAE) were reported as indicated in the included articles as in 50 51 accordance with the ICH-criteria. These include any untoward medical occurrence that at any dose results in death, is 52 life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization, results in persistent or 53 significant disability / incapacity, or is a congenital anomaly / birth defect. (26) AE definitions and severity assessments 54 55 as stated in the included publications are provided in the online supplementary appendix S4. Causality assessment of 56 SAE was performed by independent acupuncture therapists who were medical doctors who received more than 300 57 58 hours of acupuncture training and with more than ten years of intensive acupuncture practice. As the basis of this 59 assessment was limited to incomplete information provided in the articles lacking e.g. time references, the standard 60

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

3 AE risk estimates given as patients with AE per total number of patients were interpreted according to the guidelines 4 of the Council for International Organizations of Medical Sciences (CIOMS) as very common ($\geq 1/10$ patients), common 5 6 $(\geq 1/100 \text{ to} < 1/10)$, uncommon $(\geq 1/1,000 \text{ to} < 1/100)$, rare $(\geq 1/10,000 \text{ to} < 1/1,000)$, or very rare (< 1/10,000).(28) 7 8 Documentation of study characteristics included study type, country in which the study was conducted, reporter, 9 method and time point of AE assessment, complaint as well as age and gender structure of the study population, 10 average number and frequency of treatments per patient, average number of needles per treatment, needle in time, 11 12 acupuncture style, and method of needle stimulation, as well as number, gender, training, and years of experience of 13 acupuncturists. Data on patients' and acupuncturists' AE reports from the article published by Weidenhammer et al. 14 15 in 2008 were handled as two separate trials. 16

Risk of bias assessment 18

19 Included studies were assessed for risk of bias according to a checklist developed by Faillie and colleagues for 20 systematic reviews focusing on drug adverse events.(29) This checklist is applicable to RCTS, cohort studies, case-21 control studies, nested case-control studies, and systematic reviews. The questions are structured in 8 risk of bias 22 23 domains. Possible answers are "Not applicable" (n/a), "Yes" (Y), "Unclear" (U), or "No" (N). A summary risk of bias 24 assessment is provided for each domain as well as for the whole study. According to the inclusion criteria of this review, 25 26 questions concerning systematic reviews, cross-over trials, and case-control studies were not applicable. 27

28 Data analysis 29

Data were analysed using the package meta implemented in R.(30) Pooled estimates with 95% confidence intervals 30 31 (CI) for overall AE risk and risks of different types of AE were obtained from proportion meta-analyses. Random effects 32 models were calculated by the Hartung-Knapp method with arcsine transformation of proportions. Cochran Q test, 33 34 and I² statistics were used to assess the heterogeneity of included studies. Meta-analyses were performed for the 35 overall risks for an AE, for SAE, for AE requiring treatment and the risks for the different types of AE given as the 36 37 number of patients with AE per total number of patients undergoing an acupuncture series or as the number of 38 treatments with AE per total number of treatments performed. All studies reporting the respective risks were included 39 40 in the different meta-analyses. All AE that were reported separately in the articles, but that were allocated to the same 41 AE category, were treated as they had occurred in different patients or treatments, respectively. Sensitivity analyses 42 43 were performed for studies that explicitly only reported about AE that had, at the discretion of the assessors', a causal 44 relationship to acupuncture treatments. None of the articles reported the mean and variance of the number of AE per 45 treatment. Thus, the expected number of AE per treatment could not be estimated by meta-analysis but just by 46 47 considering the sum of AE relative to the sum of treatments. An additional sensitivity analysis was performed by 48 excluding AE that are usually very mild and transient or are often argued to be part of the treatment or a desired 49 50 treatment response, such as transient bleeding, needle site pain, or a flare around the needle insertion point. AE of 51 such type that were indicated by any means as significant were not excluded for this sensitivity analysis. 52

Patient and public involvement 54

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55 No patients were involved in defining the research question, the outcome measures, the design or conduct of this 56 review. No patients were asked to advise on interpretation of results. Authors will share the results during patient 57 58 seminars and information events. A concise version of the results will be made available for non-profit acupuncture 59 organisations to be presented on their webpages. 60

Results

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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)

14 Study characteristics are provided in table 1. The four largest trials with one to five hundred thousand patients treated 15 in over 750 thousand acupuncture sessions were cohort studies performed as part of the German Model Projects on 16 17 Acupuncture (Modellvorhaben Akupunktur).(33, 41, 46, 49) Three nationwide surveys from the UK (described in four 18 articles),(38-40, 48) one in-house surveillance report from Japan (51) and one summary of AE assessments nested 19 20 within three Chinese RCTs (52) included two to six thousand patients receiving over 30 thousand treatments, 21 respectively. In three surveys, two from South-Korea, (44, 45) one from Japan, (35) and one from Brazil, (32) around 22 23 one to two thousand patients were included and treated in up to 14 thousand acupuncture sessions. One nationwide 24 survey conducted in Sweden reported on the risk of AE based on data from over nine thousand acupuncture 25 26 sessions.(43) In seven studies less than 500 patients receiving maximum 3.5 thousand treatments were included; four 27 AE assessments nested within RCTS or clinical trials from China, (36, 47) Hong-Kong, (31) and Sweden, (37) one Japanese 28 29 (50) and one German survey (34) as well as one German cohort study.(42) In most studies acupuncture was used to 30 treat pain in middle aged patients. In six articles no details on the patients' condition were provided. (34, 35, 40, 43, 31 32 48, 50) Two articles reported explicitly on short-term AE after one particular treatment only. (39, 45) All but five articles 33 provided sufficient information to infer that acupuncturists had a firm medical background and / or had received 34 intensive acupuncture training. (34, 36, 37, 42, 43) One German survey also included "other practitioners" most likely 35 36 non-medical practitioners (Heilpraktiker) with non-standardized acupuncture training.(34) 37

Eight articles described AE reported by patients only (31, 32, 37-39, 45, 46, 49) and seven articles AE reported by 38 39 acupuncturists only. (33, 40, 41, 44, 46, 48, 51) As before said Weidenhammer et al. described therapists' and patients' 40 41 reports on AE separately. (46) Zhao et al. combined the AE reports from patients and acupuncturists. (52) In five articles 42 it was explicitly stated that acupuncturists recording the AE also queried their patients about any uncomfortable 43 experience during or after treatment.(34-36, 43, 50) In two trials AE were documented by an independent 44 45 assessor.(42, 47) In eight of the 22 included articles AE were reported irrespective of their relationship to 46 acupuncture, (31, 33, 34, 37, 40, 48, 51, 52) while descriptions of AE assessments in twelve articles suggest that only 47 48 AE related to the acupuncture treatment were documented, (32, 35, 36, 38, 39, 42-44, 46, 49, 50) and one article did 49 not provide information about the AE definition.(45) Further discrepancies were found in definitions of certain 50 51 reactions as therapeutically intended. For example, da Silva et al. did not count aggravation of symptoms as AE, 52 because of difficulties in determining causality as well as severity and because of common notion among practitioners 53 54 that transient worsening forms part of the acupuncture treatment. (32) In contrast White et al. reported observations 55 of aggravated symptoms as AE, but only those that were not followed by substantial improvements.(48) In contrast, 56 the other articles did not specify aggravation of symptoms further. (33-35, 37, 38, 42, 46, 49, 50) In addition, Endres et 57 58 al. did report on erythema at the needling site (which was accounted for in the present analysis), but did not include 59 it in their overall AE incidence report, as this can also be regarded as desired acupuncture reaction.(33) 60

Page	9 of 51			Patients				BMJ Open Treatments				Acupu	uncturists		AE assessment			
	1 st Author year	Country	Study type	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	
1	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	Р	SL & OQ any AE	after 3rd, 6th, 9th treatment	
2 3	da Silva 2014	Brazil	Cohort monocentric	1157 (n.i.)	n.i.	Musculoskeletal, emotional &respiratory disorders i.a.	13,884	12#)	n.i.	МА	n.i.	MD	in training	n.i.	Р	SL & OQ AE related to acu.	after each treatment	
4	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	n.i.	n.i.	12,000 (n.i.)	MD	> 140 h	n.i.	А	SL & OQ any AE	after last treatment	
5	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	
6 7	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	after each treatment; at subsequent visit	
8	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	SL AE related to acu.	after each treatment & subsequent visit	
9 10	List 1992	Sweden	RCT monocentric	29 (n.i.)	median 40**)	Craniomandibular disorder	арх. 174	≥6 /6-8w	12 avg.	MA & EA	1 (0)	n.i.	n.i.	n.i.	P	SL & OQ any AE	after last treatment	
11	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	upon recognition	
12 13	MacPherson 2004 ^A		Survey nationwide	6,348	52 ± 15	Musculoskeletal, psychological,	30,196	4.8		MA &	638		23009/0			any AE SL & OQ AE related to acu.	3 m after inclusion	
14	MacPherson 2005 ^A	UK	private practices	(4,821) 9,408 (6,961)	51	general, neurological, gyne- cological, obstetric & respiratory conditions; wellbeing	9,408	1	n.i.	EA	(406)	MD & physio- therapists	> 3 a	< 10 a 58% ≥ 10 a 42%	Р	SL imm. AE AE related to acu.	After the 1 st / one of the 1 st treatments	
15 16	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	
17	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	
18 19	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	
20	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	
21	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%	А	SL AE related to acu.	upon recognition	
22 23				503,397 (40,5235)	54 ± 16		4.2 M	8.4 (2.9)			9918					SL & FT AE related to acu.	after last treatment	
24	Weiden- hammer 2008	Germany	Cohort nationwide private clinics	882847 (n.i.)	n.i.	Chronic headache, LBP, osteoarthrosis (> 6 m)	7.9 M	n.i.	n.i.	n.i.	(3570)	MD	140 h (22% > 350 h)	n.i.	A	OQ - SAE only AE related to acu.	upon recognition	
25 26	В		F	5,998 (5,072)	55 ± 15	, , ,	apx. 51582 ^{#)}	8.6 (3.0)			9429 (n.i.)		(· · · · · · · · · · · · · · · · · · ·		Р	OQ AE related to acu.	after last treatment	
27	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	
28 29	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%	А	SL & OQ any AE	upon recognition	
30 31	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	Ρ	OQ AE related to acu.	after last treatment	
32	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%	А	OQ any AE	upon recognition	
33 34	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	
35 36	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	≥8a	> 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 P) 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

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2 According to the inclusion criteria the study objective was clearly described in all articles (Figure 2, category A). Study 3 design was clear for all but one article, which stated that data were collected in the course of 11 clinical trials without 4 further specification. (36) Also, all but one AE assessment were free of a run in period. In one RCT the safety assessment 5 6 was initiated with a short delay.(37) Both irregularities were rated as unlikely to introduce bias into AE documentation. 7 High risk for selection bias (Figure 2, category B) was identified for the four RCTs and the AE assessment in 11 clinical 8 9 trials (23% of articles), due to exclusion of patients with comorbidities or bleeding tendency. In contrast, in all surveys 10 and cohort studies (77%) the risk for selection bias was rated as unclear due to an indistinct selection of therapists and 11 12 / or patients, inclusion of voluntarily participating acupuncturists or acupuncturists from specialized medical centres 13 only. Furthermore, none of the articles stated that patients were naive to acupuncture. Risk of bias due to study 14 15 withdrawal or drop-out (Figure 2, category C) was rated as low for all RCTs and two surveys, that only reported on 16 short-term AE (27%), (39, 45) and as high for one survey (5%), because treatment was ceased for 40% of patients with 17 18 AE.(44) For the remaining studies (68%) the risk of bias due to early treatment termination was rated as unclear, as 19 withdrawals and drop-outs due to AE were not reported. The risk of information bias regarding the safety outcome 20 (Figure 2, category D) was rated as high for one study (5%) because of an exclusive documentation of repeatedly 21 22 occurring AE (37) and as unclear for all remaining studies (95%). At this, AE reporting by patients or acupuncturists 23 instead of an independent assessor was classified as an unclear risk for social desirability bias. Using only a selection 24 25 list (35, 36, 39, 44) or only open questions as AE assessment tool, (49-51), lack of reporting on the AE assessment tool 26 (43, 45, 47) or the definition of the safety outcome, and selection of the time-point of the AE assessment (only directly 27 28 after treatment, (32, 33, 43, 47) only after the last treatment initiation, (37, 38, 41, 46, 49) solely upon recognition (40, 29 44, 48, 51)) were rated as possible but unclear sources of detection bias. Further risk of information bias (Figure 2, 30 31 category E) appeared to be unclear due to poor reporting of treatment details in all but seven studies (32%).(31, 37, 32 40, 41, 47, 50, 52) Bias arising from differential care, confounder assessment and statistical methods to control for 33 34 confounding (Figure 2, category F) was rated as low, as crude AE risk estimates and not relative risks with respect to a 35 comparator group were extracted. The risk of bias due to other statistical methods (Figure 2, category G) was also 36 37 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.

48 Overall risk of acupuncture related adverse events

49 Eleven studies including 845,637 patients that assessed the overall AE risk as patients with AE among the total number 50 of patients undergoing an acupuncture series were combined in a meta-analysis. The overall risk for at least one AE 51 52 during a series of acupuncture treatments was estimated to be 9.31 (95%-Cl 5.10 to 14.62) per 100 patients treated 53 (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 54 55 14), and the total number of treatments exceeded 7.4 million. Visual inspection neither indicated an association of the 56 incidence of AE with the number of treatments per acupuncture series nor with the study type (online supplementary 57 58 appendix S5). Five studies reported the total number of acupuncture treatments with AE relative to the total number 59 of treatments performed.(32, 34, 36, 40, 42) Meta-analysis of these studies covering 55,026 treatments in total 60

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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%-Cl 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	total	Number of AE excluding bleeding, pain & flare	AE incider total	nce per 100 treatments excluding bleeding, pain & flare	Bleeding, pain, flare a needling site as % of all AE
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%

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%-Cl 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 (I² > 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	Melchart 2004	Causality	
- Death	unlikely	9	- Exacerbation of depression	possible	
 Fall or trauma, with or without fracture 	possible	4	- Hypertensive crisis	possible	
 Acute general infection with hospitalization 	unlikely	2	- Vasovagal reaction	possible	
 Allergic reaction to concomitant medication (atopy) 	possible	1	 Asthma attack with hypertension and angina 	possible	
 Stroke with hospitalization 	unlikely	3	- Pneumothorax	possible	
- Cardiovascular problems (hospital admission)	possible	3	Yamashita 1999	Causality	
 Intervertebral disk prolapse, pain exacerbation with hospital admission 	unclassifiable	5	 Hospitalization of patient with asthma because of coughing 	possible	
 Malignant parotid tumor (hospital admission) 	unlikely	1	- 1 case of deep burn that recovered after 2	possible	
- Hospitalization (unknown reasons)	unclassifiable	17	years		
Weidenhammer 2008 ther.	Causality	n	MacPherson 2004	Causality	-
- Pneumothorax	possible	5	- Low back pain in breast cancer patient,	possible	
 Suicidiation in a patient with borderline syndrome 	unlikely	1	hospital admission, disappeared without medication, since then no more LBP		
 Hypertensive crisis 	possible	1	- Car crash 2d after acupuncture, very little	unlikely	
 Syncope (vasovagal reaction) 	possible	2	sleep the night before		
 Asthma attack in a patient with asthma 	possible	1	- Skin rash and feeling ill for several weeks	possible	
- Erysipelas (one in a patient with lymphedema)	possible	2	accompanied by decrease of ME		
 Circulatory collapse (one with uncontrolled defecation and one with vertigo and paresthesia) 	possible	2	symptoms and feeling of catharsis (no treatment)		
 Circulatory reaction with amnesia 	unlikely	1			
 Tonic-clonic seizures and ophistotonus 	unlikely	1			
- Infection of the knee joint with E. coli bacteria	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.

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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 (I² 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	Sum of	Risk as patient	s with AE per 100	patients [95%-CI]	Tau ²	Number of	Sum of	Risk as treatment	s with AE per 100 tre	eatments [95%-CI]	Tau ²
1	Type of AE			overall	min	min max		studies	treatments	overall	min	max	I ²
2	Bleeding	13	1038741	4.67	0.48	25.18	0.0008	13	190661	4.92	0.03	45.45	0.0169
3	Dieeunig	15	1030741	[2.08; 8.22]	[0.32; 0.67]	[21.10; 29.50]	99.4%**	13	190001	[1.18; 11.01]	[0.02; 0.05]	[42.89; 48.03]	99.9%**
1	Needle site pain	14	1038907	3.75	0.05	44.83	0.0085	12	188661	2.43	0.01	15.75	0.0095
5	Necule site pull		1050507	[0.74; 8.94]	[0.04; 0.06]	[27.46; 62.87]	99.9%**	12	100001	[0.63; 5.35]	[0.00; 0.02]	[13.92; 17.68]	99.8%**
5				2.79	0.15	35.59	0.0494			0.13	0.00	0.90	0.0004
7	Other local AE	10	1034610	[0.02; 10.01]	[0.14; 0.16]	[23.97; 48.14]	100.0%* *	11	187566	[0.04; 0.27]	[0.00; 0.01]	[0.48; 1.46]	96.4%**
3	Vegetative			1.95	0.08	58.62	0.0012			2.24	0.00	27.87	0.0213
)	reaction	12	1036607	[0.40; 4.63]	[0.07; 0.08]	[40.52; 75.59]	99.7%**	12	188661	[0.21; 6.35]	[0.00; 0.01]	[26.97; 28.78]	99.9%**
0	Aggravation of	11	1026760	1.48	0.08	93.10	0.0017	10	172002	0.84	0.00	2.83	0.0055
	symptoms	11	1036760	[0.00; 5.90]	[0.07; 0.09]	[81.26; 99.30]	99.8%**	10	173682	[0.26; 1.75]	[0.00; 0.01]	[2.66; 3.01]	99.7%**
1	Central nervous	9	244553	1.45	0.05	37.93	0.0018	11	179253	0.20	0.01	1.08	0.0011
2	system	9	244553	[0.07; 4.51]	[0.00; 0.20]	[21.45; 55.99]	96.3%**	11	179253	[0.05; 0.46]	[0.00; 0.02]	[0.76; 1.44]	98.4%**
3	Peripheral	8	433118	0.69	0.08	27.59	0.0004	10	152813	0.19	0.00	1.46	0.0008
4	nervous system	0	455116	[0.02; 2.34]	[0.07; 0.10]	[13.14; 44.96]	98.1%**	10	152615	[0.02; 0.55]	[0.00; 0.01]	[0.84; 2.26]	98.0%**
5	Distant pain	5	241817	0.60	0.17	0.95	0.0005	4	46456	0.73	0.07	4.49	0.0085
	Distant pain	5	241017	[0.21; 1.20]	[0.09; 0.29]	[0.72; 1.21]	92.6%**	4	40450	[0.00; 5.02]	[0.00; 0.27]	[4.08; 4.91]	99.5%**
6	Gastrointestinal /			0.60	0.01	17.24	0.0008			0.15	0.01	1.18	0.0008
7	gynaecologcial	9	747559	[0.04; 1.81]	[0.01; 0.02]	[5.94; 32.83]	99.3%**	10	186125	[0.03; 0.38]	[0.00; 0.02]	[0.97; 1.41]	98.2%**
8	system			• • •						• • •			
9	Unclassified AE	10	1036307	0.57	0.07	17.85	0.0003	9	172136	0.47	0.00	5.46	0.0025
0				[0.01; 1.95]	[0.05; 0.08]	[14.29; 21.70]	99.0%**			[0.03; 1.46]	[0.00; 0.01]	[4.74; 6.23]	99.4%**
1	Headache	9	845745	0.51	0.03	13.56	0.0012	7	97592	0.04	0.00	0.14	0.0002
	Candianaaaalaa			[0.03; 1.55]	[0.03; 0.04]	[6.10; 23.38]	99.6%**			[0.01; 0.10]	[0.00; 0.01]	[0.01; 0.40]	90.3%**
2	Cardiovascular	5	739155	0.40	0.27	0.83	0.0001	3	18774	0.03	0.01	0.08	0.0001
3	system			[0.24; 0.61] 0.38	[0.25; 0.29] 0.08	[0.00; 3.21] 41.38	96.4%**			[0.00; 0.13]	[0.00; 0.04] 0.00	[0.00; 0.33]	21.2% 0.0001
4	Motor system	5	237634	[0.00; 4.79]	[0.07; 0.09]	41.38 [24.41; 59.48]	0.0011 94.6%**	5	82112	0.01 [0.00; 0.04]		0.03	0.0001 58.1%*
5	Generalized skin			0.35	0.09	[24.41; 59.48] 1.69	0.0029			[0.00; 0.04]	[0.00; 0.01]	[0.00; 0.11]	58.1%
6	reaction	2	229289	[0.00; 35.67]	[0.08; 0.10]	[0.00; 6.52]	58.2%	-					
	Needling			0.22	0.00	1.04	0.0009			0.12	0.01	0.62	0.0002
7	malpractice	7	1029871	[0.01; 0.67]	[0.00; 0.00]	[0.81; 1.30]	99.7%**	7	164146	[0.02; 0.28]	[0.00; 0.02]	[0.28; 1.10]	95.1%**
8	Emotional			0.20	0.02	1.24	0.0002			0.08	0.01	0.67	0.0004
9	interference	6	930429	[0.00; 0.81]	[0.02; 0.02]	[0.99; 1.53]	98.7%**	7	155131	[0.00; 0.27]	[0.00; 0.02]	[0.51; 0.84]	96.8%**
0	Sleeping			0.16	0.04	20.69	0.0001			[0.00, 0.27]	[0.00, 0.02]	[0.31, 0.04]	50.070
50 51	problems	5	432529	[0.00; 0.91]	[0.03; 0.05]	[8.19; 37.03]	97.1%**	-					
	AE caused by			0.14	0.00	0.96	0.0002			0.02	0.00	0.17	0.0001
2	moxibustion	4	428682	[0.00; 1.16]	[0.00; 0.00]	[0.60; 1.42]	98.3%**	4	145750	[0.00; 0.18]	[0.00; 0.01]	[0.11; 0.25]	95.0%**
33	Respiratory			0.04	0.02	0.24	0.0001			0.03	[,]	[]	
84	system	3	235637	[0.00; 0.26]	[0.01; 0.02]	[0.00; 0.96]	69.0%*	1	3535	[0.00; 0.11]			
35		1		[[],]	[]		1		[]			

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

4 To date this is the first systematic review on prospective studies that provides summary risk estimates for acupuncture 5 6 related adverse events derived from meta-analyses. The obtained results suggest that AE can be expected in every 7 tenth patient that undergoes a series of acupuncture treatments and, overall, in every 13th treatment. Minor AE were 8 9 common and represented the large majority of reported AE. About half of the reported minor AE are usually mild and 10 transient or might even be regarded as part of the acupuncture treatment or therapeutically intended reactions 11 (bleeding, needle site pain, flare around the needle site).(21) SAE can be expected rarely in about every 10,000th 12 13 patient in the course of an acupuncture series and, overall, in every 125,000th treatment. Sensitivity analyses excluding 14 studies with zero SAE incidences still suggest SAE being rare (every 7000th patient and every 60,000th treatment) 15 16 particularly in comparison to SAE risk associated with pharmacological treatments. (16, 53, 54) AE requiring treatment 17 occur uncommonly in about every 900th treatment, but additional AE are likely to also have involved medical decision-18 19 making about further diagnostics and follow-up. With meta-analyses for the overall risk of acupuncture related AE 20 covering over 845,637 patients undergoing more than 7.4 million treatments and for the risk of SAE covering more 21 22 than 1.2 million patients and 10.6 million treatments, the amount of data is equivalent to such available on the safety 23 of e.g. common analgesics. (55, 56) This work augments insights on acupuncture related adverse events from previous 24 25 reviews with either narrow eligibility criteria or focussing on case reports.(17) It includes data from the largest and 26 most rigorous trials on acupuncture safety e.g. from the large nationwide cohort studies conducted in the UK and 27 Germany which had not yet been aggregated. (33, 38-41, 46, 48, 49) Thus, our results provide rigorous support for the 28 29 previously drawn conclusion (22, 57, 58) that acupuncture is among the safe treatments in medicine with SAE occurring 30 rarely and half of the common minor AE being mild and transient. The uncommon AE requiring treatment necessitate 31 32 solid medical competence of acupuncturists. 33

³⁴ ³⁵ <u>Types of adverse events related to acupuncture and implications for medical education of acupuncturists</u>

Common minor AE were bleeding, needle site pain, other local reactions at the needling site, vegetative reactions, 36 37 aggravation of symptoms, and AE related to the central nervous system (one to five out of 100 patients). This is in line 38 with other reviews (22, 59) also on auricular (60) and paediatric acupuncture. (58) All other types of minor AE can be 39 40 regarded as uncommon (1 to 7 out of 1000 patients), despite respiratory reactions that occurred very rarely (4 out of 41 10,000 patients). SAE most often reported were pneumothorax, strong cardiovascular or vasovagal reactions, and fall 42 43 or trauma with one to three cases in one million treatments. Several other sometimes fatal SAE repeatedly described 44 in case reports were not observed in the included studies; e.g. traumatic injuries of inner organs, local and systemic 45 46 infections, subarachnoid bleeding, infective endocarditis, and cardiac tamponade.(61-65) This is likely due to the fact 47 that acupuncturists in most of the studies were well trained, as SAE are claimed to be avoidable by proper acupuncture 48 49 training and practice. Concordantly, cases of acupuncture malpractice were uncommon in the included trials. 50

51 <u>Heterogeneity between studies</u>

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.

12 A further possible cause of heterogeneity are differences in contrasting AE from therapeutically intended reactions 13 that form part of acupuncture treatment; e.g. in contrast to international consensus, (18) aggravated symptoms were 14 15 not or only in part counted as AE in two studies. (32, 48) Local reactions such as bleeding, pain, and flare at the needling 16 site that represented half of the AE reported and are referred to as beneficial signs in standard acupuncture textbooks 17 18 and by authors themselves. (20, 33) As the principle of acupuncture is to induce endogenous anti-nociceptive 19 mechanisms and anti-inflammatory humoral responses through micro-trauma of skin and tissue, it can be argued that 20 moderate local reactions are indeed desired reactions indicating an induction of regulative processes. Mild pain and a 21 22 flare at the needling site have been linked to important neurophysiological mechanisms of acupuncture.(21) 23 Additionally, aching or soreness at the needling site might be part of the intended degi sensation (propagated 24 25 sensation along the channels) supposedly related to acupuncture effectiveness.(19) The loss of small drops of blood 26 upon needle withdrawal is interpreted as a sign for the patient's constitution called "excess" or "excess heat" in TCM 27 28 terminology and was suggested not to be interpreted as AE.(67) On the other hand, standard text books explicitly 29 explain needling techniques avoiding pain and bleeding. (20, 68) This debate calls for a uniform internationally 30 31 recognized consensus on the definition of local acupuncture reactions as AE e.g. according to their quality and 32 intensity. 33

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.

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44Risk of bias in included studies

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45 Although, large prospective studies are among the most important sources of safety data, they come with the known 46 risk for information, selection, and confounding bias.(70) Risk of information bias was mostly related to poor reporting 47 48 of acupuncture regimens and the discrepancies in AE definition and assessment. This is in line with the shortcoming 49 identified for reporting of AE in acupuncture randomized controlled trials.(71) Possible causes of selection bias 50 identified were mainly voluntary participation of practitioners, unsystematic patient selection, and study conductance 51 52 in highly specialized institutions. Practical reasons make these causes of selection bias inherent to safety studies. They, 53 however, are unlikely to importantly impair external validity, considering the large number of patients and treatments, 54 55 the variety of countries in which studies were conducted, and the inclusion of different study designs. Future large 56 scale comparative safety studies along with modern statistical methods for confounder adjustment could be used to 57 58 contrast AE risks related acupuncture to AE risks associated with other treatments and to identify patient and 59 treatment characteristics associated with AE in real world clinical settings.(72) 60

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Limitations

2 First, it is debatable whether studies should be summarized irrespective of whether AE not necessarily related to 3 acupuncture or adverse reactions likely caused by acupuncture were reported. Another limitation with regard to the 4 inclusion criteria is the restriction to articles published in German or English as many studies on acupuncture are 5 6 published in Chinese. In order to provide the most comprehensive information possible respective sensitivity analyses 7 were conducted. Additionally, the risk estimates for the different types of minor adverse events are likely to be slightly 8 9 overestimated and should be interpreted as a rough indication that allows to distinguish frequent from less frequent 10 acupuncture related minor AE. In categorizing the minor AE it was disregarded that several different AE falling in one 11 12 category could have occurred in the same patient or during the same treatment. Also, calculations of risks in 13 treatments with AE per total number of treatments could not adjust for the fact that multiple AE assessments in the 14 15 same patient are not independent. Furthermore, zero incidences of certain types of AE were not available. Finally, the 16 causality assessment presented for SAE is limited to expert opinions and is only based on the information provided in 17 18 the respective article. Such an evaluation does not replace a rigorous causality assessment that would involve querying 19 patients and therapists. 20

21 <u>Clinical implications</u>

23 Patients should be informed that acupuncture commonly causes minor AE, but rarely SAE. Examples for SAE should at 24 least cover the most frequent ones, pneumothorax and strong cardiovascular or vasovagal reactions potentially 25 26 leading to fall or trauma, along with the respective incidence of 1-3 per million treatments. Patients should also be 27 made aware of the fact that great part of the minor AE are either very mild or even intended effects that indicate a 28 29 beneficial physiological reactions. However, they should be encouraged to report any prolonged discomfort or pain 30 that are to be avoided during treatment. Acupuncturists should carefully balance treatment intensity according to 31 patients' reactions in order to minimize AE. They should assess local AE upon needle withdrawal and query patients 32 33 about AE directly after treatment as well as at the subsequent visit. Therapists should be aware that, although 34 uncommon, AE requiring treatment can be expected and necessitate medical decision making. Medical competence 35 36 is also required for the indication of acupuncture in patients at high risk for AE or those in which AE could lead to 37 particular aversive outcomes such as pregnant women, elderly and patients with cardiovascular comorbidities. In 38 39 these patients acupuncture can be especially beneficial, as conventional treatments e.g. with analgesics are often 40 limited by side effects or drug interactions, but selection of acupuncture regimens needs to involve careful risk-benefit 41 42 considerations. Theses medical competences required to provide optimal patient safety should also be reflected by 43 acupuncture education standards and regulations. At this policy makers should take into account the worldwide 44 popularity of acupuncture which is likely to further increase as its scientific level of evidence has led to more than 4000 45 46 practice guidelines recommending acupuncture for different mostly pain indications.(69) 47

Conclusion

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50 Acupuncture can be considered among the safer treatments in medicine. It rarely causes SAE and the majority of the 51 52 common minor AE are very mild. AE requiring medical management are uncommon. For optimal patient safety 53 acupuncture education standards regulations should reflect that solid medical competence of acupuncturists is 54 required to manage AE properly and to minimize the risk of malpractice. Clinical and methodological heterogeneity 55 56 calls for an international consensus on AE assessment tools in acupuncture studies and criteria for differentiating 57 acupuncture related AE from therapeutically desired reactions as well as identification of patient related risk factors 58 59 for acupuncture related AE. In particular, comparative safety studies are needed to contrast acupuncture to standard 60 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.).

²⁴ ²⁵ 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.

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Page 21 of 51

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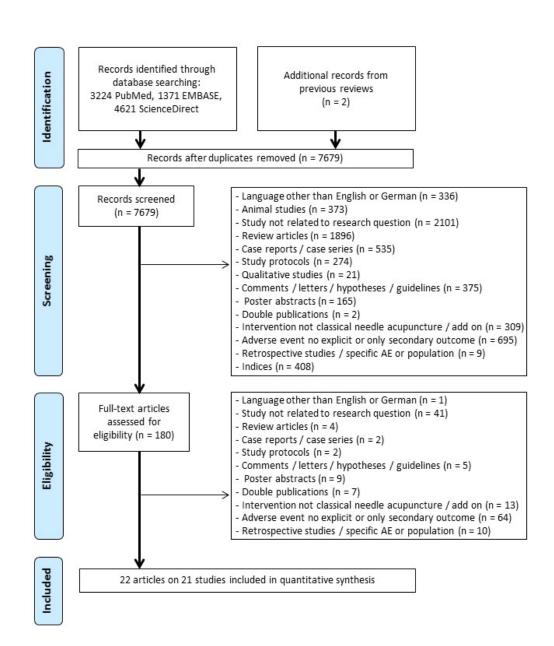
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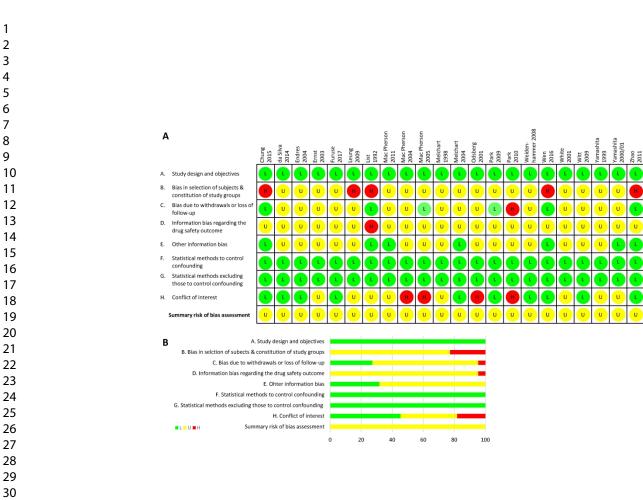
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Study	patients with AE	total patients	Risk per 100 patients	Events	95%-CI	Weight (fixed)	
Chung 2015	25	59		42.37	[30.15; 55.09]	0.0%	1.2
Wen 2016	5				[1.34; 8.45]	0.0%	2.3
Melchart 1998	34				20.48; 36.41]	0.0%	2.3
Leung 2009	6				[0.86; 4.58]	0.0%	4.2
Ernst 2003	153				32.79; 42.15]	0.0%	5.8
Zhao 2011	74				[2.97; 4.65]	0.2%	11.3
Weidenhammer 2008 pat.	560		+		[8.61; 10.09]	0.7%	13.7
MacPherson 2004	682		+		[9.99; 11.52]	0.8%	13.7
Melchart 2004	6942				[6.94; 7.26]		15.1
Witt 2009	19726				[8.49; 8.72]		15.1
Weidenhammer 2008 ther.			17 8 1		[7.69; 7.84]		15.2
Fixed effect model		845637		7.94	[7.88; 8.00]	100.0%	
Random effects model			•	9.31	[5.10; 14.62]		100.0
Heterogeneity: $I^2 = 99\%$, $\tau^2 =$	= 0.0004, <i>p</i> < 0.01	0	10 20 30 40 50	60			
Overall AE risk per acu	ipuncture treati	-	10 20 00 40 00	00		Mai	ght V
Study tr	eatments with AE	total treatments	Risk per 100 treatme	nts Even	ts 95%	-CI (fix	
Melchart 1998	106	1200	<u>+</u>	8.8	33 [7.29; 10.	50] 2.	2%
Leung 2009	8	2000	•	0.4	10 [0.17; 0.	72] 3.	6%
Ernst 2003	402	3535		11.3	37 [10.35; 12.	44] 6.	4%
da Silva 2014	1092	13884	in l	7.8	37 [7.42; 8.	32] 25.	2%
MacPherson 2001	5179	34407	*	15.0	05 [14.68; 15.	43] 62.	5%
Fixed effect model		55026	•	11.8	38 [11.61; 12.	15] 100.	0%
Random effects model				- 7.5	57 [1.43; 17.	95]	1
Heterogeneity: $I^2 = 100\%$, τ^2	= 0.0103, <i>p</i> < 0.01		0 5 10 15	20	•		
Overall risk for AE rel	lated to acupur				series		
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Study	patients with AE	total patients	Risk per 100 patients	Events	95%-CI	(iixea) (randon
Wen 2016	5	120		4.17	[1.34; 8.45]	0.0%	1.7
Leung 2009	6	254		2.36	[0.86; 4.58]	0.0%	3.2
Weidenhammer 2008 pat.	560	5998		9.34	[8.61; 10.09]	0.7%	16.8
MacPherson 2004	682	6348			[9.99; 11.52]	0.8%	17.0
	6942		*		[6.94; 7.26]	11.6%	20.3
Melchart 2004					[8.49; 8.72]	27.2%	20.5
	19/26						
Melchart 2004 Witt 2009 Weidenhammer 2008 ther.	19726 39078	503397	*	7.76	[7.69; 7.84]	59.7%	20.6
Witt 2009		503397 843080	*		[7.69; 7.84] [7.88; 8.00] 1		20.6

D Overall risk for AE related to acupuncture per treatment

Weight Weight

Study	treatments with AE	total treatments	Risk pe	er 100 tr	eatments	Event	s 95%-Cl	(fixed)	(random)
Leung 2009 da Silva 2014 MacPherson 2001	8 1092 5179	2000 * 13884 34407	×	+		0.4 7.8 15.0		27.6%	33.1% 33.4% 33.4%
Fixed effect model Random effects mode Heterogeneity: $I^2 = 1009$		50291 	10	20	30		9 [11.71; 12.28] 8 [0.00; 38.76]		

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7	A Overall SAE risk among patients undergoing an acupuncture series Weight Weight
-	Study patients with SAE total patients Risk per 10000 patients Events 95%-Cl (fixed) (random)
8	Wen 2016 0 120 + → 0.00 [0.00; 79.82] 0.0% 0.4% Leung 2009 0 254 + → 0.00 [0.00; 37.76] 0.0% 0.8%
9	Yamashita 2000 0 391 → 0.00 [0.00; 24.54] 0.0% 1.2%
10	da Silva 2014 0 1157 0.00 [0.00; 8.30] 0.1% 3.3% Zhao 2011 0 1968 0.00 [0.00; 4.88] 0.2% 5.1%
1	Furuse 2017 0 2180 0.00 [0.00; 4.40] 0.2% 5.5% Yamashita 1999 2 5008 3.99 [0.38; 11.44] 0.4% 9.5%
2	MacPherson 2004 3 6348 Melchart 2004 6 97733 - 0.61 [0.22; 1.20] 8.2% 20.5%
	Endres 2004 45 190924 - 2.36 [1.72; 3.10] 16.1% 21.1% Weidenhammer 2008 ther. 17 882847 0.19 [0.11; 0.29] 74.3% 21.6%
	Fixed effect model 1188930 0.43 [0.32; 0.56] 100.0%
	Random effects model 1.01 [0.23; 2.33] 100.0%
	Heterogeneity: $l^2 = 88\%$, $\tau^2 < 0.0001$, $p < 0.01$ 0 2 4 6 8 10 12 14
	B Overall SAE risk per acupuncture treatment Weight Weight
	Study treatments with SAE total treatments Risk per 1e+06 treatments Events 95%-CI (fixed) (random)
	Yamashita 2000 0 1441 → 0.00 0.00 0.00: 666.31] 0.0% 0.4% Wen 2016 0 1680 → 0.00 0.00: 571.54] 0.0% 0.5%
	Leung 2009 0 2000 + 0.00 [0.00; 480.11] 0.0% 0.6%
	Park 2010 0 3071 → 0.00 [0.00; 312.69] 0.0% 0.9% da Silva 2014 0 13884 → 0.00 [0.00; 69.17] 0.1% 3.5%
	Furuse 2017 0 14039 0.00 [0.00; 68.41] 0.1% 3.6% MacPherson 2004 3 30196 > 99.35 [18.73; 243.56] 0.3% 6.3%
	White 2001 0 31822 0.00 [0.00; 30.18] 0.3% 6.5% MacPherson 2001 0 34407 0.00 [0.00; 27.91] 0.3% 6.8%
	Zhao 2011 0 39360 0.00 [0.00; 24.40] 0.4% 7.4%
	Yamashita 1999 2 65482 30.54 [2.88; 87.54] 0.6% 9.8% Melchart 2004 6 760000 7.89 [2.84; 15.48] 7.1% 17.2%
	Endres 2004 45 1770000 - 25.42 [18.54; 33.39] 16.5% 18.0% Weidenhammer 2008 ther. 17 7945000 2.14 [1.24; 3.28] 74.2% 18.4%
	Fixed effect model 10712382 4.75 [3.53; 6.14] 100.0%
	Random effects model 7.98 [1.39; 20.00] 100.0%
	Heterogeneity: $l^2 = 85\%$, $\tau^2 < 0.0001$, $p < 0.01$ 0 20 40 60 80 100120140
	C Overall risk for SAE related to acupuncture among patients undergoing a treatment series Weight Weight
	Study patients with SAE total patients Risk per 10000 patients Events 95%-CI (fixed) (random)
	Wen 2016 0 120 → 0.00 [0.00; 79.82] 0.0% 0.2% Leung 2009 0 254 → 0.00 [0.00; 37.76] 0.0% 0.3%
	Yamashita 2000 0 391 → 0.00 [0.00; 24.54] 0.0% 0.5% da Silva 2014 0 1157 0.00 [0.00; 8.30] 0.1% 1.5%
	Furuse 2017 0 2180 0.00 [0.00; 4.40] 0.2% 2.7%
	MacPherson 2004 3 6348 4.73 [0.89; 11.58] 0.6% 7.2% Melchart 2004 6 97733 - 0.61 [0.22; 1.20] 9.9% 37.3%
	Weidenhammer 2008 ther. 17 882847 0.19 [0.11; 0.29] 89.1% 50.3%
	Fixed effect model 991030 0.23 [0.15; 0.34] 100.0% Random effects model 0.45 [0.06; 1.18] 100.0%
	Heterogeneity: $l^2 = 41\%$, $t^2 < 0.0001$, $p = 0.11$ 0 2 4 6 8 10 12 14
	D Overall risk for SAE related to acupuncture per treatment Weight Weight
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	Yamashita 2000 0 1441 → 0.00 [0.00; 666.31] 0.0% 0.3%
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	Park 2010 0 3071 → 0.00 [0.00; 312.69] 0.0% 0.6% da Silva 2014 0 13884 - 0.00 [0.00; 69.17] 0.2% 2.6%
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Petra

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80336 Munich, Germany

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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

Batathon under and the date of award

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

PROSPERO International prospective register of systematic reviews

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 comparison 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:

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Prospective study

Primary outcome is the risk of acupuncture related adverse events

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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.

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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 metaanalysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

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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.

u health are. 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

NHS National Institute for Health Research

PROSPERO International prospective register of systematic reviews

No

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2 3

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12 13

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15 16 17

18

- Service delivery No
- Synthesis of qualitative studies No
- Systematic review Yes
- Other
- No

Health area of the review

10	
19	Alcohol/substance misuse/abuse
20	No
21 22	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
23	Cancer
24 25	No
25 26	Cardiovascular
20	No
28	
29	Care of the elderly No
30	
31	Child health
32	No
33	Complementary therapies
34 35	Yes
35 36	COVID-19
37	No
38	Crime and justice
39	No
40	Dental
41	No
42	Digestive system
43 44	No
44 45	Ear, nose and throat
46	No
47	Education
48	No
49	Endocrine and metabolic disorders
50	No
51 52	Eye disorders
53	No
55	General interest
55	No
56	Genetics
57	No
58	Health inequalities/health equity
59 60	No
00	

1	PROSPERO
2	International prospective register of systematic reviews
3 4	Infections and infestations
5	No
6 7	International development No
8	Mental health and behavioural conditions
9	No
10	Musculoskeletal
11	No
12	Neurological
13 14	No
14	Nursing
16	No
17	Obstetrics and gynaecology
18	
19	Oral health
20	No
21 22	Palliative care
22	No
24	Perioperative care
25	No
26	Physiotherapy
27 28	No
28 29	No Oral health No Palliative care No Perioperative care No Physiotherapy No Pregnancy and childbirth No
30	No
31	Public health (including social determinants of health)
32	No
33	Rehabilitation
34 35	
36	Respiratory disorders
37	No Respiratory disorders No Service delivery No Skin disorders No Social care No Surgery
38	Service delivery
39	No
40 41	Skin disorders
41	No
43	Social care
44	No
45	Surgery
46	No
47 48	Tropical Medicine
49	No
50	Urological
51	No
52	Wounds, injuries and accidents
53 54	No
54 55	Violence and abuse
56	No
57	
58	

31. Language.

58

59 60

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

NHS 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

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Review_Ongoing

PROSPERO

39. Any additional information.

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

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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.

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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	<u>.</u>		
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	ection/topic # Checklist item					
Risk of bias across studies	15	15 Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).				
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.					
Study characteristics	18	or each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide ne citations.				
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).				
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.				
Synthesis of results	21	21 Present results of each meta-analysis done, including confidence intervals and measures of consistency.				
			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			

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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 For peer review.only - http://bmjopen.bmj.com/site/about/guidelines.xhtml For more information, visit: <u>www.prisma-statement.org</u>. Page 2 of 2

Item No	Recommendation	Reported on Page No
Reporting o	f 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 o	f 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 o	f 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 o	f 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

MOOSE Checklist for Meta-analyses of Observational Studies

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

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Bleeding			
Bleeding		Small hemorrhage	Ecchymosis or hematoma
Bleeding at needling		Lesion of blood vessel	accompanied by pain
Mild / transient / mi	-	Bruising	 Ecchymosis or hematoma without
 Subcutaneous bleed 	ing	Bruising at needling site	pain Petechia or ecchymosis
Hematoma		Mild / transient bruising	• Fetecina of eccliphiosis
 Minor hematoma Subsutaneous / subsutaneous / subsutaneo	orficial homotoma	Heavy bruisingSubcutaneous bruise	
Subcutaneous / superior		• Subcutarieous bruise	
Local painPain		 Pain upon insertion / stimulation 	 Mild pain at the acupuncture site
Needle (-site) pain		 Pain while needle was in place 	more than one hour after treatment
Pain where needle v	vas inserted / at	 Pain upon needle withdrawal at the 	 Pain disappearing after > 3 days
the site of the needl		acupuncture point	 Chest pain (pneumothorax ruled out)
punctured region		Pain after needle was removed	Electroacupuncture problems e.g. to
 Mild / transient pair 	at needling site	Remaining / residual needle site pain	strong current resulting in pain
 Severe / strong / sig 	-	 Prolonged / unacceptable pain at 	Local muscle pain
needling site		needle site	• Unknown pain
Other local AE			
Wheal		 Inflammation at application site 	 Significant rash on abdomen few day
 (Local) swelling 		• Itch	after acupuncture
Redness		Itching and redness	Cellulitis after treatment of
• Flare		 Itching in the punctured region 	edematous leg
 Localized erythema 		 Itching and erythema (suspected 	 Edema in m. tibialis with anterior toe
 Needle-site / local sl 	kin reaction	contact dermatitis)	lifting weakness (fully resolved)
 (Skin) irritation at ac 	upuncture point	 Local allergic reaction (uticaria) 	 Other local AE (around the
 Skin infection 		 Needle allergy 	acupuncture site)
 Local (skin) infectior 	l	 Allergic phenomena / reaction 	
Central nervous system		\sim	
 Aphasia 		• Vertigo	 Disturbed vision
 Dizziness 		 Disorientation (length unspecified, 1 	 Spontaneous sensory perceptions
 Mild / transient dizz 	iness	h, 1 day)	 Shivering
 Imbalance 		 Severe disorientation 	 Seizure shortly after treatment
 Severe dizziness, ver 	tigo or loss of	Disturbed speech	Tremor
balance		Slurred speech	
Peripheral nervous syst			
 Cold sensation at ne 	-	Prolonged deqi	Hypaesthesia with numbness for
 Feeling of acupunction 	ire point at	Strong acupuncture or heavy	three days
contralateral arm		sensation	Insensibility Itabian aires & peoples tipoling on
Paraesthesia	i-	Hypaesthesia	 Itching, pins & needles, tingling or human consetion
 Temporary paraesth 	esia	Numbness	burning sensationNerve irritation
Tingling Tingling	urning	 Numbness in upper extremity Numbness and unusual sensation 	Nerve initiation Neuritis
 Tingling, prickling, b dysesthesia 	urring,	 Severe stiffness or numbness 	Neuritis
Aggravation of symptor	2	• Severe stimless of humbless	
•••	115	• Transient aggravation of symptoms	• Worsoning of condition (after
 Aggravation Aggravation of complexity 	laints / evisting	 Transient aggravation of symptoms Aggravation of existing symptoms 	 Worsening of condition (after removing needles)
ailment / existing sy		followed by improvement	Headache and or facial pain
 Unexpected, severe 	•	Deterioration / exacerbation of	 pressure and or tension in the teeth
worsening of sympto		symptoms	Increased pain
 Aggravation of symp 		 General aggravation of symptoms 	
acupuncture session	-	Worsening of health state	
Vegetative nervous syst			
 (Generalized) sweat 		 Abnormal tiredness 	 Significant / severe drowsiness
 Isolated sweating of 	-	 Severe / significant tiredness or 	 Drowsiness not causing hazard
 Mild sweating 		exhaustion	Prolonged drowsiness (one day, one
 Flushed cheeks and 	body warmth	Lethargy	week)
 Hot flash 		• Dazed	Drowsiness or restlessness
 Feeling of warm / he 	eat / cold	 Vasovagal reaction: collapse, 	 Orthostatic problems
Coldness / feeling co		dizziness, nausea & vomiting	Malaise
Freezing		 Unconsciousness 	 Poor concentration
• (Feeling of) fatigue		• Fainting	 Dry lips / mouth
 Extreme feeling of fa 	atigue	 Faint / dizzy 	Xerostomia
 Feeling tired (mild till 	ansient)	 Feel faint / drowsy 	 Hunger / thirst
 Tiredness and exhau 		 Feel faint (significant) 	

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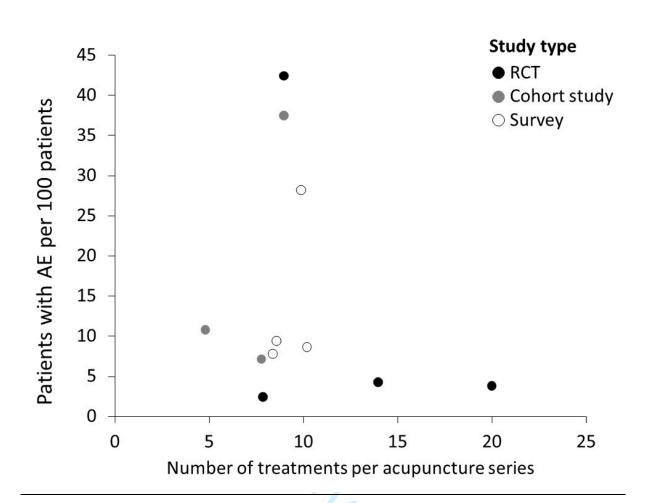
Motor system		• Joint problems
 Cramp General muscle tenderness 	 Heavy legs Knee went weak 	 Joint problems Restricted movement
		Stiffness
Muscle spasm / tension / weakness Distant pain	Weakness in legs / legs or arms	• sunness
Pain / ache / discomfort other than	 Mild transient pain not at 	Generalized muscle pain
at needling site	needling site	• Other / unspecified pain / aches
 Reactive pain at other body sites 	Chest pain / tightness	
Gastrointestinal / gynaecological system		
Nausea	• Tiredness next day after ten hours of	 Increased peristalsis
 Mild and transient nausea 	diarrhoea (significant)	Loss of appetite
Severe nausea	Stomach ache	Other gastrointestinal complaints
Vomiting	 Abdominal distension 	 Increased haemorrhage during
Severe vomiting	 Impaired bowel function 	menses
Constipation	Digestive problems	 Menstrual problems
• Diarrhoea	• Entero- / gastrospasm	·
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	ů.	
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 ange
Anxiety	Discomfort	at practitioner
 Anxiety and panic (up to one hour) 	 Restlessness or nervousness 	• Fear
 Significant panic with sensation of 	 Disorientation, anxiety, nervousness, 	 Grief / crying / tearful
heat and sweatiness	insomnia or emotional	 Needle phobia, anxiety and rage
 Severe panic / agitation / depression 	 Emotional /psychological reaction 	 (Severe) nightmares
with anxiety	 (Uncontrolled) euphoria 	 Other mood swings
 Depressed emotional state or 	 Significant emotional release (manic, 	
neurovegetative dystonia	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 	 Failure to remove needle(s) 	
treatment room for too long	 Forgotten / dropped needle 	
Broken needle	 Needle lost or forgotten 	
 Stuck or bent needle 		
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)
• Fever	 Concomitant diseases of recent 	adverse events
• Angina	appearance	 other negative reactions
 Eventuation 	 Change of taste 	 Unknown due to incomplete record
 Eye irritation 	 Change of weight / weight reduction 	form

n are reported verbatim or in spirit in order to provide an overview of the different wordings concerning AE type and severity. Slashes indicate that 56 expressions were also used separately. Terms in brackets indicate that such terms were not used in all of the descriptors with otherwise similar 57 58 wording.

59

Study	AE definition (<i>direct quotes</i> with eventual comments)	Severity rating (<i>direct quotes</i> 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 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 hospit 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/un 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. pneumothora 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 Reportto 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 neede treatment, received from the study office an additional, more detailed standardised questionnain 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 the 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."
	"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



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

Page 49 of 51

BMJ Open

				Risk as patients with AE per 100 patients [95%-CI]								
<u>)</u> ; ;	Study	Total number of patients	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]		
0	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]	
1 2	Leung 2009	254	2.36 [0.86; 4.58]									
3 4	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]				
5	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]
6 7	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]	
8 9	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]
20	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]
21 22	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]
23 24	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]
25	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]
6 7	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]
28 29	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]
0	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]
1 2	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]
3 4	tau²		0.0008	0.0085	0.0494	0.0012	0.0017	0.0018	0.0004	0.0005	0.0008	0.0003
5 6	l²		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%]
57 18	p-value Q-test		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Page 5	50 of 51
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Study	Total number				•	s with AE per 100				
	of patients	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]		k		0,13 [0,06; 0,24]		0,07 [0,02; 0,15]
MacPherson 2004	6348	1.21 [0.9585; 1.50] 0.04				1,04 [0,81; 1,30] 0,25	1,24 [0,99; 1,53]	0,74 [0,54; 0,97]	0,44 [0,29; 0,62]	
Melchart 2004	97733	[0.0275; 0.05]				[0,22; 0,28] 0,00	0,04	0,04	0,00	
Endres 2004	190924	0.52	0.27	0,08	0,09	[0,00; 0,00] 0,01	[0,03; 0,05] 0,09	[0,03; 0,05]	[0,00; 0,00] 0,01	0,02
Witt 2009 Weidenhammer	229230 503397	[0.4944; 0.55] 0.03	[0.25; 0.29] 0.42	[0,07; 0,09]	[0,08; 0,10]	[0,00; 0,01] 0,28	[0,08; 0,11] , 0,0197	[0,03; 0,05]	[0,00; 0,01]	[0,01; 0,02]
2008 therapists	505557	[0.0287; 0.04]	[0.40; 0.43]	0.00	0.00	[0,27; 0,30]	[0,02; 0,02]	0.05	0.00	0.02
Fixed effect		0.12 [0.11; 0.13]	0.40	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
l ²		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

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1			Risk as treatments with AE per 100 treatments [95%-CI]										
2 3	Study	Total number of treatments	Bleeding	Pain	Other local AE	Vegetative nervous system	Aggravation of symptoms	Central nervous system	Peripheral nervous system	Distant pain	Gastrointestinal /gynaecologcial AE	Unclassified AE	
4 5	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]			
6 7	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]		
8 9	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]		
10	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]	
11 12	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]	
13 14	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]	
15	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]	
16 17	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]	
18 19	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]	
19 20	Leung 2009	2000	0.40 [0.17; 0.72]										
21 22	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]	
23	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]	
24 25	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]	
26 27	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	0.03 [0.02; 0.04]	0.96 [0.87; 1.05]	0.08 [0.07; 0.09]	0.23 [0.20; 0.25]	
28 29	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]	
30	tau²		0.0169	0.0095	0.0004	0.0213	0.0055	0.0011	0.0008	0.0085	0.0008	0.0025	
31 32 33	l²		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%]	
34	p-value Q-test		< 0.0001	< 0.0001	0.0001	< 0.0001	< 0.0001	0.0001	< 0.0001	0.0001	0.0001	0.0001	
35			•										

Page 52	of 51
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amashita 2000		1	system	Motor system	skin reaction	malpractice	interference	Sleeping problems	AE	system
	1441	0.14 [0.01; 0.40]				0.62 [0.28; 1.10]				
aSilva2014	13884					0.24 [0.16; 0.33]				
lelchart1998	1200		0.08 [0.00; 0.33]				0.08 [0.00; 0.33]			
lacPherson2005	9408						0.67 [0.51; 0.84]			
uruse2017	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]	
rnst2003	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]
dsberg2001	9277	0.05 [0.02; 0.11]		0.01 [0.00; 0.04]			0.04 [0.01; 0.10]			
amashita 1999	65482					0.04 [0.03; 0.06]	0.01 [0.00; 0.02]		0.01 [0.00; 0.02]	
ark2009	1095									
eung2009	2000									
ark2010	3071	0.03 [0.00; 0.13]		0.10 [0.02; 0.24]		0.10 [0.02; 0.24]				
/hite2001	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]	
lacPherson2001	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]	
xed 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]	
andom 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]
ıu²		0.0002	0.0001	0.0001		0.0002	0.0004		0.0001	
		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%]	
value Q-test		0.0001	0.2811	0.0489		0.0001	0.0001		0.0001	
nline supplen	nentary app	endix <u>S7: R</u> isl	<u>ks for differ</u> er	nt types of ad	verse event	<u>s per 100 tr</u> ea	atments as rep	orted in sir	ngle studies	

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

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

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Word count

- 6426
- 52 53 54 55 56 57 58

Page	3 of 50 BMJ Open
1	Abstract
2 3	Objective
3 4 5	Overview on risks for acupuncture related adverse events (AE).
6	Design
7 8	Systematic review and meta-analysis of prospective studies.
9 10	Data sources
11 12	Pubmed, Scopus, and EMBASE from inception date to September 15, 2019.
12 13 14	Eligibility criteria for selecting studies
15	Prospective studies assessing AE caused by needle acupuncture in humans as primary outcome published in English
16 17	or German
18 19	Data extraction and synthesis
20	Two independent researchers selected articles, extracted the data and assessed study quality. Overall risks and risks
21 22	for different AE categories were obtained from random effects meta-analyses.
23 24	Main outcomes
25 26	Overall risk for minor AE and serious AE (SAE) per patients and per treatments
27 28	Results
20 29	A total of 7679 publications were identified. Twenty-two articles reporting on 21 studies were included. Meta-analyses
30 31	suggest at least one AE occurring in 9.31% (95%-CI 5.10 to 14.62; 11 studies) of patients undergoing an acupuncture
32	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%-
33 34	CI 0.23 to 2.33; 11 studies) per 10,000 patients and 7.98 (95%-Cl 1.39 to 20.00; 14 studies) per 1 million treatments,
35	for AE requiring treatment 1.14 (95%-CI 0.00 to 7.37; eight studies) per 1000 patients. Heterogeneity was substantial
36 37	(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
38	that are argued to represent intended acupuncture reaction. AE definitions and assessments varied largely.
39 40	Conclusion
41	Acupuncture can be considered among the safer treatments in medicine. SAE are rare, and most common minor AE
42 43	are very mild. AE requiring medical management are uncommon but necessitate medical competence to assure
44	patient safety. Clinical and methodological heterogeneity call for standardized AE assessments tools, clear criteria for
45 46	differentiating acupuncture related AE from therapeutically desired reactions, and identification of patient related risk
47 48	factors for AE.
49	PROSPERO registration number
50 51	CRD42020151930
52	
53 54	
55	Keywords
56 57	Adverse effects, adverse reactions, meta-analysis, safety, risk, pneumothorax
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59 60	
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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

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Introduction

2 Acupuncture describes the insertion of fine needles at defined points on the patients' body for therapeutic or 3 preventive purposes. It is used worldwide with growing popularity. In the EU acupuncture was identified as the most 4 5 frequently provided method of complementary and alternative medicine (CAM) with 80,000 physicians and 16,380 6 non-medical practitioners.(1) In the UK alone 2.3 million traditional acupuncture treatments are carried each year.(2) 7 In the US the number of acupuncturists doubled between 2002 and 2012.(3) The effectiveness of acupuncture is 8 9 supported by level 1a evidence e.g. for chronic musculoskeletal pain and headache, (4-6) post-operative pain, (7, 8) 10 post-operative nausea and vomiting,(9) as well as allergic rhinitis.(10) Furthermore, promising evidence exists for its 11 12 potential role in the treatment of numerous other indications, such as stroke rehabilitation,(11) depression,(12) 13 aromatase inhibitor induced arthralgia,(13) and asthma.(14) Thus, acupuncture offers a non-pharmacological 14 15 treatment option for various highly prevalent conditions with great disease burden and significant health economic 16 impact. Long-term pharmacological treatment of these conditions is often associated with substantial side effects. (15, 17 18 16) Consequently, also risk estimates on acupuncture related adverse events (AE) are required for evidence-based risk 19 benefit considerations that are essential for clinical decision making. 20

21 However, uncertainty remains about acupuncture safety. AE related to acupuncture are repeatedly and controversially 22 discussed both in scientific literature as well as in public media. An overview of systematic reviews in 2017 (17) 23 24 illustrates that many of the previous reviews on the safety of acupuncture just summarized case reports or case series. 25 In turn, those reviews including studies that do allow for AE frequency estimation, such as cohort studies and large 26 27 RCTs, mostly only addressed certain types of AE, particular patient groups, restricted acupuncture regimens, or certain 28 countries. These data are surely important for clinical decision making in particular cases, but leave the overall risk of 29 30 acupuncture related AE in the general population obscure. Additionally, debate exists about differentiating AE from 31 therapeutically intended reactions that are claimed to form part of the acupuncture treatment. For example, 32 33 international consensus exists that aggravation of symptoms represents an AE, because disease burden increases. 34 However, transient worsening of symptoms followed by long-term improvements can be interpreted as a so called 35 healing crisis in complementary and alternative medicine.(18) In contrast, such consensus is still missing for local 36 37 reactions, such as small bleedings upon needle withdrawal, needling pain, and flare around the needling site. These 38 are also interpreted as beneficial signs by acupuncture experts and in standard text books and have been linked to 39 40 neurophysiological mechanisms of acupuncture. Accordingly, quality and intensity of these events should be 41 considered when classifying them as AE.(19-21) 42

43 The last review on prospective studies on AE related to acupuncture with high external validity dates back to 2001,(22) 44 did not meta-analytically summarize AE risk estimates, and did not assess the quality of included studies. In addition, 45 46 inconsistency and incompleteness of reporting in primary studies hampered the drawing of firm conclusions on 47 acupuncture safety. Since then various large-scale clinical trials and nationwide surveys on acupuncture safety have 48 49 been conducted. 50

Therefore, it was the aim of this review to provide an up to date summary of prospective trials that were particularly 52 designed to evaluate AE related to needle acupuncture with manual or electrical stimulation and in combination with or without moxibustion. 54

Methods

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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 **BMJ** Open

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

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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 10 11 related AE.(17) "Acupuncture" and "adverse effects" are MeSH terms. 12

13 In- and exclusion criteria 14

We included articles reporting on prospective studies (cohort studies, RCTs, surveys or surveillances) assessing AE 15 16 associated with needle acupuncture involving manual or electrical stimulation combined with or without moxibustion 17 in humans as their primary outcome. Case reports and case series were not included. Only articles published in English 18 19 or German were included. Publications on assessments of acupuncture point injection therapies or non-penetrating 20 acupuncture point stimulation, such as laser acupuncture, acupressure, or transcutaneous electrical nerve stimulation 21 22 (TENS), were excluded. We also excluded articles reporting solely on moxibustion or restricted acupuncture regimens 23 such as press-needle, auricular, or one-point acupuncture. Trials focusing just on one type of acupuncture related AE 24 25 or just on a narrowly defined patient population were excluded. 26

27 Article selection and data extraction

28 Article selection was performed independently by two reviewers (WZ and PB, TS and PB, or LM and PB). Retrieved 29 30 records were first screened for eligibility by abstract. Full texts were obtained for the remaining articles. Final decision 31 about eligibility was obtained by consensus of all four reviewers. 32

33 Estimates of overall risks and risks for each reported type of AE were extracted as absolute numbers of patients with 34 AE per total number of patients and treatments with AE per total number of treatments. Data concerning AE from 35 36 sham- or placebo-acupuncture treatments were not extracted. The different types of AE were assigned to one of the 37 following categories: bleeding, local pain, other local AE, distant pain, central nervous system, peripheral nervous 38 39 system, vegetative nervous system, motor system, gastrointestinal / gynaecological system, cardiovascular system, 40 respiratory system, generalized skin reactions, headache, emotional interference, sleeping problems, AE related to 41 42 moxibustion, needling malpractice, aggravation of symptoms, other or unclassified AE (online supplementary 43 appendix S3). 44

45 Following the differentiation between AE and adverse drug reactions (ADR) defined by the International Conference 46 on Harmonization (ICH) of Good Clinical Practice, (26) articles were classified into reports on adverse events 47 48 irrespective of their causal relationship to acupuncture and adverse reactions for which a causal relationship was a 49 reasonable possibility. Serious adverse events (SAE) were reported as indicated in the included articles as in 50 51 accordance with the ICH-criteria. These include any untoward medical occurrence that at any dose results in death, is 52 life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or 53 significant disability / incapacity, or is a congenital anomaly / birth defect. (26) AE definitions and severity assessments 54 55 as stated in the included publications are provided in the online supplementary appendix S4. Causality assessment of 56 SAE was performed by independent acupuncture therapists who were medical doctors who received more than 300 57 58 hours of acupuncture training and with more than ten years of intensive acupuncture practice. As the basis of this 59 assessment was limited to incomplete information provided in the articles, lacking e.g. time references, the standard 60

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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 (\geq 1/10 patients), common (\geq 1/100 to < 1/10), uncommon (\geq 1/1,000 to < 1/100), rare (\geq 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.

17 <u>Risk of bias assessment</u>

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.

28 Data analysis

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29 Data were analysed using the package meta implemented in R.(30) Pooled estimates with 95% confidence intervals 30 31 (CI) for overall AE risk and risks of different types of AE were obtained from proportion meta-analyses. Random effects 32 models were calculated by the Hartung-Knapp method with arcsine transformation of proportions. Cochran Q test, 33 34 and I² statistics were used to assess the heterogeneity of included studies. Meta-analyses were performed for the 35 overall risks for an AE, for SAE, for AE requiring treatment, and the risks for the different types of AE. Separate meta-36 37 analyses were conducted for AE risks given as the number of patients with AE per total number of patients undergoing 38 an acupuncture series and AE risks given as the number of treatments with AE per total number of treatments 39 performed. All studies reporting the respective risks were included in the different meta-analyses. All AE that were 40 41 reported separately in the articles, but that were allocated to the same AE category, were treated as they had occurred 42 in different patients or treatments, respectively. Sensitivity analyses were performed for studies that explicitly only 43 44 reported about AE that had, at the discretion of the assessors', a causal relationship to acupuncture treatments. None 45 of the articles reported the mean and variance of the number of AE per treatment. Thus, the expected number of AE 46 47 per treatment could not be estimated by means of a meta-analysis but just by considering the sum of AE relative to 48 the sum of treatments. An additional sensitivity analysis was performed by excluding AE that are usually very mild and 49 50 transient or are often argued to be part of the treatment or a desired treatment response, such as transient bleeding, 51 needle site pain, or a flare around the needle insertion point. AE of such type that were indicated by any means as 52 significant were not excluded from this sensitivity analysis. 53

55 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

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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)

14 Study characteristics are provided in table 1. The four largest trials, which included 100,000 to 500,000 patients treated 15 in over 750,000 acupuncture sessions, were cohort studies performed as part of the German Model Projects on 16 17 Acupuncture (Modellvorhaben Akupunktur).(33, 41, 46, 49) Three nationwide surveys from the UK (described in four 18 articles),(38-40, 48) one in-house surveillance report from Japan,(51) and one summary of AE assessments nested 19 20 within three Chinese RCTs (52) included two to six thousand patients receiving over 30 thousand treatments, 21 respectively. In three surveys, two from South-Korea, (44, 45) one from Japan, (35) and one from Brazil, (32) around 22 23 one to two thousand patients were included and treated in up to 14 thousand acupuncture sessions. One nationwide 24 survey conducted in Sweden reported on the risk of AE based on data from over nine thousand acupuncture 25 26 sessions.(43) In seven studies less than 500 patients receiving a maximum of 3.5 thousand treatments were included; 27 four AE assessments nested within RCTs or clinical trials from China, (36, 47) Hong-Kong, (31) and Sweden, (37) one 28 29 Japanese (50) and one German survey (34) as well as one German cohort study.(42) In most studies acupuncture was 30 used to treat pain in middle aged patients. In six articles no details on the patients' condition were provided.(34, 35, 31 32 40, 43, 48, 50) Two articles reported explicitly on short-term AE after one particular treatment only. (39, 45) All but five 33 articles provided sufficient information to infer that acupuncturists had a firm medical background and / or had 34 received intensive acupuncture training.(34, 36, 37, 42, 43) One German survey also included "other practitioners" 35 36 most likely non-medical practitioners (Heilpraktiker) with non-standardized acupuncture training.(34) 37

Eight articles described AE reported by patients only (31, 32, 37-39, 45, 46, 49) and seven articles AE reported by 38 39 acupuncturists only. (33, 40, 41, 44, 46, 48, 51) As before said Weidenhammer et al. described therapists' and patients' 40 reports on AE separately. (46) Zhao et al. combined the AE reports from patients and acupuncturists. (52) In five articles 41 42 it was explicitly stated that acupuncturists recording the AE also queried their patients about any uncomfortable 43 experience during or after treatment.(34-36, 43, 50) In two trials AE were documented by an independent 44 45 assessor.(42, 47) In eight of the 22 included articles AE were reported irrespective of their relationship to 46 acupuncture, (31, 33, 34, 37, 40, 48, 51, 52) while descriptions of AE assessments in twelve articles suggest that only 47 48 AE related to the acupuncture treatment were documented, (32, 35, 36, 38, 39, 42-44, 46, 49, 50) and one article did 49 not provide information about the AE definition.(45) Further discrepancies were found in definitions of certain 50 51 reactions as therapeutically intended. For example, da Silva et al. did not count aggravation of symptoms as AE, 52 because of difficulties in determining causality as well as severity and because of common notion among practitioners 53 54 that transient worsening forms part of the acupuncture treatment. (32) In contrast White et al. reported observations 55 of aggravated symptoms as AE, but only those that were not followed by substantial improvements.(48) In contrast, 56 the other articles did not specify aggravation of symptoms further. (33-35, 37, 38, 42, 46, 49, 50) In addition, Endres et 57 58 al. did report on erythema at the needling site (which was accounted for in the present analysis), but did not include 59 it in their overall AE incidence report, as this can also be regarded as desired acupuncture reaction.(33) 60

Page	9 of 50					Patients		Trea	BMJ C)pen		Acupi	uncturists			AE assessme	ent
	1 st Author year	Country	Study type	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
1	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	Р	SL & OQ any AE	after 3rd, 6th, 9th treatment
2 3	da Silva 2014	Brazil	Cohort monocentric	1157 (n.i.)	n.i.	Musculoskeletal, emotional &respiratory disorders i.a.	13,884	12#)	n.i.	МА	n.i.	MD	in training	n.i.	Р	SL & OQ AE related to acu.	after each treatment
4	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.	А	SL & OQ any AE	after last treatment
5	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
6 7	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	after each treatment; at subsequent visit
8	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	SL AE related to acu.	after each treatment & subsequent visit
9 10	List 1992	Sweden	RCT monocentric	29 (n.i.)	median 40**)	Craniomandibular disorder	арх. 174	≥6 /6-8w	12 avg.	MA & EA	1 (0)	n.i.	n.i.	n.i.	P	SL & OQ any AE	after last treatment
11	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%	А	SL & OQ any AE	upon recognition
12 13	MacPherson 2004 ^A		Survey nationwide	6,348 (4,821)	52 ± 15	Musculoskeletal, psychological, general, neurological, gyne-	30,196	4.8		MA &	638	MD & physio-	2340370	< 10 a 58%		SL & OQ AE related to acu.	3 m after inclusion
14	MacPherson 2005 ^A	UK	private practices	9,408 (6,961)	51	cological, obstetric & respiratory conditions; wellbeing	9,408	1	n.i.	EA	(406)	therapists	> 3 a	≥ 10 a 42%	Р	SL imm. AE AE related to acu.	After the 1 st / one of the 1 st treatments
15 16	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
17	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
18 19	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
20	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
21 22	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%	А	SL AE related to acu.	upon recognition
22 23				503,397 (40,5235)	54 ± 16	,	4.2 M	8.4 (2.9)			9918				_	SL & FT AE related to acu.	after last treatment
24	Weiden- hammer 2008	Germany	Cohort nationwide private clinics	882847 (n.i.)	n.i.	Chronic headache, LBP, osteoarthrosis (> 6 m)	7.9 M	n.i.	n.i.	n.i.	(3570)	MD	140 h (22% > 350 h)	n.i.	A	OQ - SAE only AE related to acu.	upon recognition
25 26	в			5,998 (5,072)	55 ± 15		apx. 51582 ^{#)}	8.6 (3.0)			9429 (n.i.)				Р	OQ AE related to acu.	after last treatment
27	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
28 29	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%	А	SL & OQ any AE	upon recognition
30 31	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	Ρ	OQ AE related to acu.	after last treatment
32	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%	А	OQ any AE	upon recognition
33 34	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
35 36	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	≥8a	> 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 P) 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

1 2 According to the inclusion criteria the study objective was clearly described in all articles (Figure 2, category A). Study 3 design was clear for all but one article which stated that data were collected in the course of 11 clinical trials without 4 further specification. (36) Furthermore, all but one AE assessment were free of a run in period. In one RCT the safety 5 6 assessment was initiated with a short delay.(37) Both irregularities were rated as unlikely to introduce bias into the 7 AE documentation. High risk for selection bias (Figure 2, category B) was identified in the four RCTs and the AE 8 9 assessment in 11 clinical trials (23% of articles), due to exclusion of patients with comorbidities or bleeding tendency. 10 In contrast, in all surveys and cohort studies (77%) the risk for selection bias was rated as unclear due to an indistinct 11 12 selection of therapists and / or patients, inclusion of voluntarily participating acupuncturists or acupuncturists from 13 specialized medical centres only. Furthermore, none of the articles stated that patients were naive to acupuncture. 14 15 Risk of bias due to study withdrawal or drop-out (Figure 2, category C) was rated as low for all RCTs and two surveys, 16 that only reported on short-term AE (27%), (39, 45) and as high for one survey (5%), because treatment was ceased 17 18 for 40% of the patients with AE.(44) For the remaining studies (68%) the risk of bias due to early treatment termination 19 was rated as unclear, as withdrawals and drop-outs due to AE were not reported. The risk of information bias regarding 20 the safety outcome (Figure 2, category D) was rated as high for one study (5%) because of an exclusive documentation 21 22 of repeatedly occurring AE (37) and as unclear for all remaining studies (95%). At this, AE reporting by patients or 23 acupuncturists instead of an independent assessor was classified as an unclear risk for social desirability bias. Further 24 25 possible but unclear sources of detection bias were the sole use of a selection list (35, 36, 39, 44) or the sole use of 26 open questions as AE assessment tool,(49-51) lack of reporting on the AE assessment tool (43, 45, 47), unclear 27 28 definition of the safety outcome, and the time-point of the AE assessment (only directly after treatment, (32, 33, 43, 29 47) only after the last treatment initiation, (37, 38, 41, 46, 49) solely upon recognition (40, 44, 48, 51)). Further risk of 30 31 information bias (Figure 2, category E) appeared to be unclear due to poor reporting of treatment details in all but 32 seven studies (32%).(31, 37, 40, 41, 47, 50, 52) Bias arising from differential care, confounder assessment, and 33 statistical methods to control for confounding (Figure 2, category F) was rated as low, as crude AE risk estimates and 34 35 not relative risks with respect to a comparator group were extracted. The risk of bias due to other statistical methods 36 37 (Figure 2, category G) was also rated as low, as reporting of AE incidence was clear and well-structured in all articles. 38

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.

48 Overall risk of acupuncture related adverse events

47

49 Eleven studies including 845,637 patients that assessed the overall AE risk as patients with AE among the total number 50 of patients undergoing an acupuncture series were combined in a meta-analysis. The overall risk for at least one AE 51 52 during a series of acupuncture treatments was estimated to be 9.31 (95%-Cl 5.10 to 14.62) per 100 patients treated 53 (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 54 55 14), and the total number of treatments exceeded 7.4 million. Visual inspection neither indicated an association of the 56 incidence of AE with the number of treatments per acupuncture series nor with the study type (online supplementary 57 58 appendix S5). Five studies reported the total number of acupuncture treatments with AE relative to the total number 59 of treatments performed.(32, 34, 36, 40, 42) Meta-analysis of these studies covering 55,026 treatments in total 60

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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%-Cl 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	total	Number of AE excluding bleeding, pain & flare	AE incidei total	nce per 100 treatments excluding bleeding, pain & flare	Bleeding, pain, flare a needling site as % of all AE
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%

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%-Cl 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

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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 (I² > 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	Melchart 2004	Causality	
- Death	unlikely	9	- Exacerbation of depression	possible	
 Fall or trauma, with or without fracture 	possible	4	- Hypertensive crisis	possible	
 Acute general infection with hospitalization 	unlikely	2	- Vasovagal reaction	possible	
 Allergic reaction to concomitant medication (atopy) 	possible	1	 Asthma attack with hypertension and angina 	possible	
 Stroke with hospitalization 	unlikely	3	- Pneumothorax	possible	
- Cardiovascular problems (hospital admission)	possible	3	Yamashita 1999	Causality	
 Intervertebral disk prolapse, pain exacerbation with hospital admission 	unclassifiable	5	 Hospitalization of patient with asthma because of coughing 	possible	
 Malignant parotid tumor (hospital admission) 	unlikely	1	- 1 case of deep burn that recovered after 2	possible	
- Hospitalization (unknown reasons)	unclassifiable	17	years		
Weidenhammer 2008 ther.	Causality	n	MacPherson 2004	Causality	
- Pneumothorax	possible	5	- Low back pain in breast cancer patient,	possible	
 Suicidiation in a patient with borderline syndrome 	unlikely	1	hospital admission, disappeared without medication, since then no more LBP		
 Hypertensive crisis 	possible	1	- Car crash 2d after acupuncture, very little	unlikely	
 Syncope (vasovagal reaction) 	possible	2	sleep the night before		
 Asthma attack in a patient with asthma 	possible	1	- Skin rash and feeling ill for several weeks	possible	
- Erysipelas (one in a patient with lymphedema)	possible	2	accompanied by decrease of ME		
 Circulatory collapse (one with uncontrolled defecation and one with vertigo and paresthesia) 	possible	2	symptoms and feeling of catharsis (no treatment)		
 Circulatory reaction with amnesia 	unlikely	1			
 Tonic-clonic seizures and ophistotonus 	unlikely	1			
- Infection of the knee joint with E. coli bacteria	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.

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Acupuncture related adverse events requiring treatment

2 Eight studies determining the number of patients with AE requiring treatment during an acupuncture series included 3 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 4 1000 patients for the risk to suffer from an AE that required treatment when undergoing an acupuncture series (Figure 5 6 5). (31, 32, 36, 41, 46, 47, 49, 50) Also here, heterogeneity was substantial (I² 100%). Two articles, that had defined AE 7 requiring treatment as an SAE criterion, reported lower incidences (two and six events per 100,000 patients) (41, 46) 8 9 than other two articles, reporting on AE requiring treatment without referring to SAE (1.7 and 2.2 in 100 patients).(31, 10 49) 11

1213 Risk of different types of minor adverse events

14 Overall risk for the different types of minor AE (categorization see online supplementary appendix S3) were estimated 15 in separated meta-analyses as patients with AE per total number of patients undergoing a treatment series or as 16 17 treatments with AE per total number of treatments (Table 4). Risks estimated in single studies (online supplementary 18 appendix S6 and S7) varied largely for all types of minor AE. Most frequent and commonly occurring minor AE with 19 20 summary risk estimates between 1% and 5% of patients undergoing an acupuncture series were bleeding events, pain 21 at the needling site, other local AE, vegetative reactions, aggravation of symptoms, and events related to the central 22 23 nervous system. Summary risk estimates for bleeding events, needle site pain, vegetative reactions, and aggravation 24 of symptoms also ranged from 1% to 5% of treatments, while meta-analysis of symptoms related to the central nervous 25 26 system per acupuncture treatment resulted in a risk of two in 1000 treatments. AE estimated to be uncommon with 27 summary risk estimates of one to seven out of 1000 patients undergoing an acupuncture series were symptoms of the 28 29 peripheral nervous system, pain distant to the needling site, gastrointestinal or gynaecological symptoms, headache, 30 cardiovascular symptoms, affection of the motor system, generalized skin reactions, adverse emotional reactions, and 31 sleeping problems. Symptoms affecting the peripheral nervous system, distant pain, as well as gastrointestinal or 32 33 gynaecological symptoms were estimated to occur in one to seven out of 1000 treatments; headache, cardiovascular, 34 and motor symptoms as well as adverse emotional reactions only in one to eight out of 10,000 treatments. The risk 35 36 for respiratory AE was estimated to be rare with a summary risk estimate of four out of 10,000 patients undergoing 37 an acupuncture series and three out of 10,000 treatments. Summary risk estimates for AE caused by therapists' 38 39 malpractice and burns caused by moxibustion were one to two in 1000 patients undergoing an acupuncture series and 40 two in 10,000 to one in 1000 treatments, respectively. 41

42 Some of the studies showed outlying incidences for particular types of minor AE. List et al. observed at least one 43 vegetative reaction in the course of an acupuncture series for craniomandibular disorder in over half of the patients 44 45 (58.6%),(37) and MacPherson et al. reported vegetative reactions after over a quarter of treatments (27.9%).(39) 46 These findings exceed the frequency of vegetative reactions of up to 13.6% of patients identified in the remaining 47 48 studies and was mainly based on patient reports of abnormal tiredness after treatment. List et al. also report the 49 highest incidence of aggravation of symptoms with 93% of CMD patients as well as the highest frequency of needle 50 site pain with 44.8 % of patients. This was followed by an RCT with 32.2% of patients suffering needle site pain (31) 51 52 and a cohort study among chronic pain patients of which 10% suffered aggravation of symptoms after receiving 53 acupuncture. (42) The remaining 19 articles reported incidences smaller than 3% for aggravation of symptoms and 14% 54 55 for needle site pain. 56

Type of AE	Number of	Sum of	Risk as patients with AE per 100 patients [95%-CI]		Tau ²	Number of	Sum of	Risk as treatments	Risk as treatments with AE per 100 treatments [95%-CI]			
Type of AE	studies	patients	overall	min	max	I ²	studies	treatments	overall	min	max	1 ²
Bleeding	13	1038741	4.67	0.48	25.18	0.0008	13	190661	4.92	0.03	45.45	0.0169
bleeding	15	1056741	[2.08; 8.22]	[0.32; 0.67]	[21.10; 29.50]	99.4%**	15	190001	[1.18; 11.01]	[0.02; 0.05]	[42.89; 48.03]	99.9%*
Needle site pain	14	1038907	3.75	0.05	44.83	0.0085	12	188661	2.43	0.01	15.75	0.0095
Needle site pain	14	1038907	[0.74; 8.94]	[0.04; 0.06]	[27.46; 62.87]	99.9%**	12	188001	[0.63; 5.35]	[0.00; 0.02]	[13.92; 17.68]	99.8%*
			2.79	0.15	35.59	0.0494			0.13	0.00	0.90	0.0004
Other local AE	10	1034610	[0.02; 10.01]	[0.14; 0.16]	[23.97; 48.14]	100.0%* *	11	187566	[0.04; 0.27]	[0.00; 0.01]	[0.48; 1.46]	96.4%*
Vegetative	12	1036607	1.95	0.08	58.62	0.0012	12	188661	2.24	0.00	27.87	0.0213
reaction	12	1030007	[0.40; 4.63]	[0.07; 0.08]	[40.52; 75.59]	99.7%**	12	188001	[0.21; 6.35]	[0.00; 0.01]	[26.97; 28.78]	99.9%*
Aggravation of	11	1036760	1.48	0.08	93.10	0.0017	10	173682	0.84	0.00	2.83	0.0055
symptoms	11	1030700	[0.00; 5.90]	[0.07; 0.09]	[81.26; 99.30]	99.8%**	10	173082	[0.26; 1.75]	[0.00; 0.01]	[2.66; 3.01]	99.7%*
Central nervous	9	244553	1.45	0.05	37.93	0.0018	11	179253	0.20	0.01	1.08	0.001
system	5	244555	[0.07; 4.51]	[0.00; 0.20]	[21.45; 55.99]	96.3%**	11	179255	[0.05; 0.46]	[0.00; 0.02]	[0.76; 1.44]	98.4%*
Peripheral	8	433118	0.69	0.08	27.59	0.0004	10	152813	0.19	0.00	1.46	0.0008
nervous system	0	455116	[0.02; 2.34]	[0.07; 0.10]	[13.14; 44.96]	98.1%**	10	132013	[0.02; 0.55]	[0.00; 0.01]	[0.84; 2.26]	98.0%*
Distant pain	5	241817	0.60	0.17	0.95	0.0005	4	46456	0.73	0.07	4.49	0.008
-	5	241017	[0.21; 1.20]	[0.09; 0.29]	[0.72; 1.21]	92.6%**	-	40450	[0.00; 5.02]	[0.00; 0.27]	[4.08; 4.91]	99.5%*
Gastrointestinal /			0.60	0.01	17.24	0.0008			0.15	0.01	1.18	0.000
gynaecologcial	9	747559	[0.04; 1.81]	[0.01; 0.02]	[5.94; 32.83]	99.3%**	10	186125	[0.03; 0.38]	[0.00; 0.02]	[0.97; 1.41]	98.2% [°]
system			0.57	0.07	17.85	0.0003			0.47	0.00	5.46	0.002
Unclassified AE	10	1036307	[0.01; 1.95]	[0.05; 0.08]	[14.29; 21.70]	99.0%**	9	172136	[0.03; 1.46]	[0.00; 0.01]	[4.74; 6.23]	99.4%*
			0.51	0.03	13.56	0.0012			0.04	0.00	0.14	0.0002
Headache	9	845745	[0.03; 1.55]	[0.03; 0.04]	[6.10; 23.38]	99.6%**	7	97592	[0.01; 0.10]	[0.00; 0.01]	[0.01; 0.40]	90.3%*
Cardiovascular			0.40	0.27	0.83	0.0001			0.03	0.01	0.08	0.000
	5	739155	[0.24; 0.61]	[0.25; 0.29]	[0.00; 3.21]	96.4%**	3	18774	[0.00; 0.13]	[0.00; 0.04]	[0.00; 0.33]	21.2%
system			0.38	0.08	41.38	90.4% 0.0011			0.01	0.00	0.03	0.000
Motor system	5	237634	[0.00; 4.79]	[0.07; 0.09]	[24.41; 59.48]	94.6%**	5	82112	[0.00; 0.04]	[0.00; 0.01]	[0.00; 0.11]	58.1%
Generalized skin			0.35	0.09	1.69	0.0029			[0.00, 0.04]	[0.00, 0.01]	[0.00, 0.11]	J0.170
reaction	2	229289	[0.00; 35.67]	[0.08; 0.10]	[0.00; 6.52]	58.2%	-					
Needling			0.22	0.00	1.04	0.0009			0.12	0.01	0.62	0.0002
malpractice	7	1029871	[0.01; 0.67]	[0.00; 0.00]	[0.81; 1.30]	99.7%**	7	164146	[0.02; 0.28]	[0.00; 0.02]	[0.28; 1.10]	95.1%*
Emotional			0.20	0.02	1.24	0.0002			0.08	0.01	0.67	0.0004
interference	6	930429	[0.00; 0.81]	[0.02; 0.02]	[0.99; 1.53]	98.7%**	7	155131	[0.00; 0.27]	[0.00; 0.02]	[0.51; 0.84]	96.8%*
Sleeping			0.16	0.04	20.69	0.0001			[0:00] 0:11	[0.00, 0.01]	[0:01) 0:0 :]	501070
problems	5	432529	[0.00; 0.91]	[0.03; 0.05]	[8.19; 37.03]	97.1%**	-					
AE caused by			0.14	0.00	0.96	0.0002			0.02	0.00	0.17	0.000
moxibustion	4	428682	[0.00; 1.16]	[0.00; 0.00]	[0.60; 1.42]	98.3%**	4	145750	[0.00; 0.18]	[0.00; 0.01]	[0.11; 0.25]	95.0%*
Respiratory			0.04	0.02	0.24	0.0001			0.03	[]	[]	/0
system	3	235637	[0.00; 0.26]	[0.01; 0.02]	[0.00; 0.96]	69.0%*	1	3535	[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

4 To date this is the first systematic review on prospective studies that provides summary risk estimates for acupuncture 5 6 related adverse events derived from meta-analyses. The obtained results suggest that AE can be expected in every 7 tenth patient that undergoes a series of acupuncture treatments and, overall, in every 13th treatment. Minor AE were 8 9 common and represented the large majority of reported AE. About half of the reported minor AE are usually mild and 10 transient or might even be regarded as part of the acupuncture treatment or therapeutically intended reactions 11 (bleeding, needle site pain, flare around the needle site).(21) SAE can be expected rarely in about every 10,000th 12 13 patient in the course of an acupuncture series and, overall, in every 125,000th treatment. Sensitivity analyses excluding 14 studies with zero SAE incidences still suggest SAE being rare (every 7000th patient and every 60,000th treatment) 15 16 particularly in comparison to SAE risk associated with pharmacological treatments. (16, 53, 54) AE requiring treatment 17 occur uncommonly in about every 900th treatment, but additional AE are likely to also have involved medical decision-18 19 making about further diagnostics and follow-up. With meta-analyses for the overall risk of acupuncture related AE 20 covering over 845,637 patients undergoing more than 7.4 million treatments and for the risk of SAE covering more 21 22 than 1.2 million patients and 10.6 million treatments, the amount of data is equivalent to that on the safety of e.g. 23 common analgesics.(55, 56) This work augments insights on acupuncture related adverse events from previous 24 25 reviews with either narrow eligibility criteria or focussing on case reports.(17) It includes data from the largest and 26 most rigorous trials on acupuncture safety e.g. from the large nationwide cohort studies conducted in the UK and 27 Germany which had not yet been aggregated. (33, 38-41, 46, 48, 49) Thus, our results provide rigorous support for the 28 29 previously drawn conclusion (22, 57, 58) that acupuncture is among the safe treatments in medicine with SAE occurring 30 rarely and half of the common minor AE being mild and transient. The uncommon AE requiring treatment necessitate 31 32 solid medical competence of acupuncturists. 33

³⁴ ³⁵ <u>Types of adverse events related to acupuncture and implications for medical education of acupuncturists</u>

Common minor AE were bleeding, needle site pain, other local reactions at the needling site, vegetative reactions, 36 37 aggravation of symptoms, and AE related to the central nervous system (one to five out of 100 patients). This is in line 38 with other reviews (22, 59) also on auricular (60) and paediatric acupuncture. (58) All other types of minor AE can be 39 40 regarded as uncommon (1 to 7 out of 1000 patients), despite respiratory reactions that occurred very rarely (4 out of 41 10,000 patients). SAE most often reported were pneumothorax, strong cardiovascular or vasovagal reactions, and fall 42 43 or trauma with one to three cases in one million treatments. Several other sometimes fatal SAE repeatedly described 44 in case reports were not observed in the included studies; e.g. traumatic injuries of inner organs, local and systemic 45 46 infections, subarachnoid bleeding, infective endocarditis, and cardiac tamponade.(61-65) This is likely due to the fact 47 that acupuncturists in most of the studies were well trained, as SAE are claimed to be avoidable by proper acupuncture 48 49 training and practice. Concordantly, cases of acupuncture malpractice were uncommon in the included trials. 50

51 <u>Heterogeneity between studies</u>

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.

12 A further possible cause of heterogeneity are differences in contrasting AE from therapeutically intended reactions 13 that form part of acupuncture treatment; e.g. in contrast to international consensus, (18) aggravated symptoms were 14 15 not or only in part counted as AE in two studies. (32, 48) Local reactions such as bleeding, pain, and flare at the needling 16 site, that represented half of the AE reported, are referred to as beneficial signs in standard acupuncture textbooks 17 18 and by authors themselves. (20, 33) As the principle of acupuncture is to induce endogenous anti-nociceptive 19 mechanisms and anti-inflammatory humoral responses through micro-trauma of the skin and tissue, it can be argued 20 that moderate local reactions are indeed desired reactions indicating an induction of regulative processes. Mild pain 21 22 and a flare at the needling site have been linked to important neurophysiological mechanisms of acupuncture.(21) 23 Additionally, aching or soreness at the needling site might be part of the intended degi sensation (propagated 24 25 sensation along the channels) supposedly related to acupuncture effectiveness.(19) The loss of small drops of blood 26 upon needle withdrawal is interpreted as a sign for the patient's constitution called "excess" or "excess heat" in TCM 27 28 terminology and was suggested not to be interpreted as AE.(67) On the other hand, standard text books explicitly 29 explain needling techniques avoiding pain and bleeding. (20, 68) This debate calls for a uniform internationally 30 31 recognized consensus on the definition of local acupuncture reactions as AE e.g. according to their quality and 32 intensity. 33

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.

43 Risk of bias in included studies

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45 Although, large prospective studies are among the most important sources of safety data, they come with the known 46 risk for information, selection, and confounding bias.(70) Risk of information bias was mostly related to poor reporting 47 48 of acupuncture regimens and the discrepancies in AE definition and assessment. This is in line with the shortcoming 49 identified for reporting of AE in acupuncture randomized controlled trials.(71) Possible causes of selection bias 50 identified were mainly voluntary participation of practitioners, unsystematic patient selection, and study conductance 51 52 in highly specialized institutions. Practical reasons make these causes of selection bias inherent to safety studies. They, 53 however, are unlikely to importantly impair external validity, considering the large number of patients and treatments, 54 55 the variety of countries in which studies were conducted, and the inclusion of different study designs. Future large 56 scale comparative safety studies along with modern statistical methods for confounder adjustment could be used to 57 58 contrast AE risks related acupuncture to AE risks associated with other treatments and to identify patient and 59 treatment characteristics associated with AE in real world clinical settings.(72) 60

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Limitations

2 First, it is debatable whether studies should be summarized irrespective of whether AE not necessarily related to 3 acupuncture or adverse reactions likely caused by acupuncture were reported. In order to provide the most 4 comprehensive information possible respective sensitivity analyses were conducted. Another limitation with regard 5 6 to the inclusion criteria is the restriction to articles published in German or English as many studies on acupuncture 7 are published in Chinese. Additionally, the risk estimates for the different types of minor adverse events are likely to 8 9 be slightly overestimated and should be interpreted as a rough indication that allows to distinguish frequent from less 10 frequent acupuncture related minor AE. In categorizing the minor AE it was disregarded that several different AE falling 11 12 in one category could have occurred in the same patient or during the same treatment. Also, calculations of risks in 13 treatments with AE per total number of treatments could not adjust for the fact that multiple AE assessments in the 14 15 same patient are not independent. Furthermore, zero incidences of certain types of AE were not available. Finally, the 16 causality assessment presented for SAE is limited to expert opinions and is only based on the information provided in 17 18 the respective article. Such an evaluation does not replace a rigorous causality assessment that would involve querying 19 patients and therapists. 20

21 <u>Clinical implications</u>

23 Patients should be informed that acupuncture commonly causes minor AE, but rarely SAE. Examples for SAE should at 24 least cover the most frequent ones, pneumothorax and strong cardiovascular or vasovagal reactions potentially 25 26 leading to fall or trauma, along with the respective incidence of 1-3 per million treatments. Patients should also be 27 made aware of the fact that great part of the minor AE are either very mild or even intended effects that indicate a 28 29 beneficial physiological reactions. However, they should be encouraged to report any prolonged discomfort or pain 30 that are to be avoided during treatment. Acupuncturists should carefully balance treatment intensity according to 31 patients' reactions in order to minimize AE. They should assess local AE upon needle withdrawal and query patients 32 33 about AE directly after treatment as well as at the subsequent visit. Therapists should be aware that, although 34 uncommon, AE requiring treatment can be expected and necessitate medical decision making. Medical competence 35 36 is also required for the indication of acupuncture in patients at high risk for AE or those in which AE could lead to 37 particular aversive outcomes, such as pregnant women, elderly and patients with cardiovascular comorbidities. In 38 39 these patients acupuncture can be especially beneficial, as conventional treatments e.g. with analgesics are often 40 limited by side effects or drug interactions, but selection of acupuncture regimens needs to involve careful risk-benefit 41 42 considerations. Theses medical competences required to provide optimal patient safety should also be reflected by 43 acupuncture education standards and regulations. At this policy makers should take into account the worldwide 44 popularity of acupuncture which is likely to further increase as its scientific level of evidence has led to more than 4000 45 46 practice guidelines recommending acupuncture for different mostly pain indications.(69) 47

Conclusion

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50 Acupuncture can be considered among the safer treatments in medicine. It rarely causes SAE and the majority of the 51 52 common minor AE are very mild. AE requiring medical management are uncommon. For optimal patient safety 53 acupuncture education standards regulations should reflect that solid medical competence of acupuncturists is 54 required to manage AE properly and to minimize the risk of malpractice. Clinical and methodological heterogeneity 55 56 calls for an international consensus on AE assessment tools in acupuncture studies and criteria for differentiating 57 acupuncture related AE from therapeutically desired reactions as well as identification of patient related risk factors 58 59 for acupuncture related AE. In particular, comparative safety studies are needed to contrast acupuncture to standard 60 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 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.

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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.

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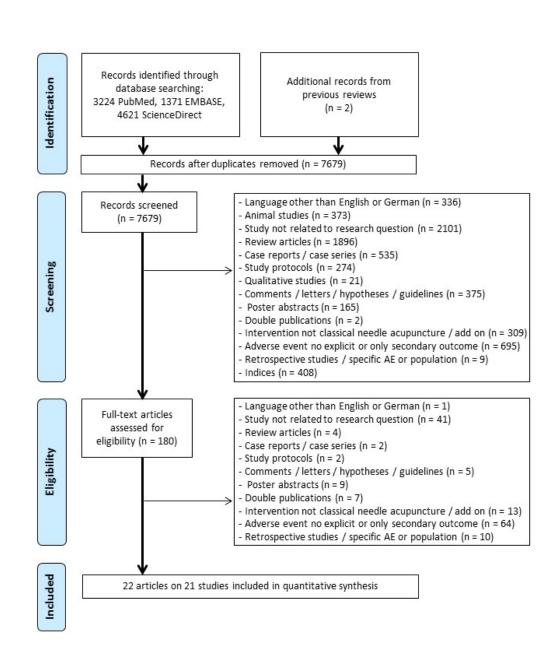
Page 21 of 50

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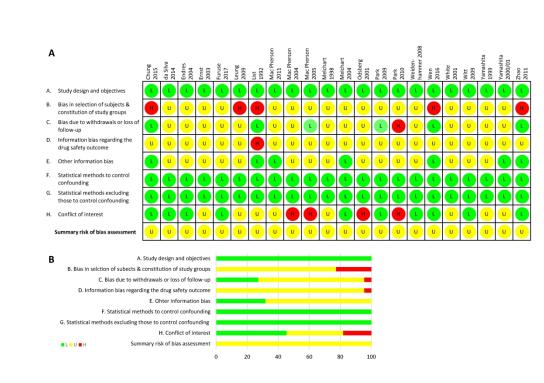
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6	A Overall AE risk among patients undergoing an acupuncture series
7	Study patients with AE total patients Risk per 100 patients Events 95%-CI (fixed) (random)
8	
9	Chung 2015 25 59 42.37 [30.15; 55.09] 0.0% 1.2% Wen 2016 5 120 4.17 [1.34; 8.45] 0.0% 2.3%
10	Melchart 1998 34 121 28.10 [20.48; 36.41] 0.0% 2.3% Leung 2009 6 254 2.36 [0.86; 4.58] 0.0% 4.2%
11	Ernst 2003 153 409 - 37.41 [32.79; 42.15] 0.0% 5.8%
12	Zhao 2011 74 1968 + 3.76 [2.97; 4.65] 0.2% 11.3% Weidenhammer 2008 pat. 560 5998 + 9.34 [8.61; 10.09] 0.7% 13.7%
13	MacPherson 2004 682 6348 - 10.74 [9.99; 11.52] 0.8% 13.7%
14	Melchart 2004 6942 97733 7.10 [6.94; 7.26] 11.6% 15.1% Witt 2009 19726 229230 8.61 [8.49; 8.72] 27.1% 15.1%
	Weidenhammer 2008 ther. 39078 503397 7.76 [7.69; 7.84] 59.5% 15.2%
15	Fixed effect model 845637 7.94 [7.88; 8.00] 100.0%
16	Random effects model \bullet 9.31 [5.10; 14.62] 100.0% Heterogeneity: $l^2 = 99\%$, $\tau^2 = 0.0004$, $p < 0.01$
17	0 10 20 30 40 50 60
18	B Overall AE risk per acupuncture treatment Weight Weight
19	Study treatments with AE total treatments Risk per 100 treatments Events 95%-CI (fixed) (rando
20	Melchart 1998 106 1200 - 8.83 [7.29; 10.50] 2.2% 19.6
21	Leung 2009 8 2000 * 0.40 [0.17; 0.72] 3.6% 19.9 Ernst 2003 402 3535 * 11.37 [10.35; 12.44] 6.4% 20.0
22	da Silva 2014 1092 13884 🖷 7.87 [7.42; 8.32] 25.2% 20.
23	MacPherson 2001 5179 34407 + 15.05 [14.68; 15.43] 62.5% 20.2
23	Fixed effect model 55026 11.88 [11.61; 12.15] 100.0%
	Random effects model Heterogeneity: $l^2 = 100\%$, $\tau^2 = 0.0103$, $p < 0.01$
25	0 5 10 15 20
26	C Overall risk for AE related to acupuncture among patients undergoing a treatment series
27	Weight Weight Study patients with AE total patients Risk per 100 patients Events 95%-CI (fixed) (random)
28	Wen 2016 5 120 4.17 [1.34; 8.45] 0.0% 1.7%
29	Leung 2009 6 254 2.36 [0.86; 4.58] 0.0% 3.2%
30	Weidenhammer 2008 pat. 560 5998 9.34 [8.61; 10.09] 0.7% 16.8% MacPherson 2004 682 6348 10.74 [9.99; 11.52] 0.8% 17.0%
31	Melchart 2004 6942 97733 ** 7.10 [6.94; 7.26] 11.6% 20.3%
32	Witt 2009 19726 229230 8.61 [8.49; 8.72] 27.2% 20.5% Weidenhammer 2008 ther. 39078 503397 7.76 [7.69; 7.84] 59.7% 20.6%
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34	Random effects model 8.23 [6.42; 10.25] 100.0%
	Heterogeneity: $l^2 = 98\%$, $\tau^2 = 0.0002$, $p < 0.01$ 0 2 4 6 8 10 12
35	D. Overall risk for AF related to acupuncture per treatment
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37	Leung 2009 8 2000 • 0.40 [0.17; 0.72] 4.0% 33.
38	da Silva 2014 1092 13884 🖷 7.87 [7.42; 8.32] 27.6% 33.4
39	MacPherson 2001 5179 34407 • 15.05 [14.68; 15.43] 68.4% 33.4
40	Fixed effect model 50291 11.99 [11.71; 12.28] 100.0%
41	Random effects model Heterogeneity: $l^2 = 100\%$, $\tau^2 = 0.0133$, $p < 0.01$ 6.08 [0.00; 38.76] 100.0
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Leung 2009	6	254		2.36 [0.8	6; 4.58] 0.0%	4.2%
Ernst 2003	153	409		37.41 [32.79	9; 42.15] 0.0%	5.8%
Zhao 2011	74	1968 +		3.76 [2.9	7: 4.65] 0.2%	11.3%
Weidenhammer 2008 pat.	560	5998	+	9.34 [8.6		13.7%
MacPherson 2004	682	6348	+	10.74 [9.99		13.7%
Melchart 2004	6942	97733 *		7.10 [6.9		15.1%
Witt 2009	19726	229230	1	8.61 [8.4		15.1%
Weidenhammer 2008 the	r. 39078	503397		7.76 [7.6	9; 7.84] 59.5%	15.2%
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da Silva 2014	1092	13884	-		[7.42; 8.32] 25.2%	
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Heterogeneity: I ² = 100%, τ C Overall risk for AE re Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Melchart 2004 Witi 2009 Weidenhammer 2008 their Fixed effect model Random effects model Heterogeneity: I ² = 98%, τ ² O Overall risk for AE re Study	elated to acupunction patients with AE tot 5 6 560 682 6942 19726 r. 39078	aire among pa al patients 120 254 5998 6348 97733 229230 503397 843080 0 ure per treatr tal treatments	tients undergoing a tr Risk per 100 patients	teatment series Events 4.17 [1.34] 2.36 [0.86] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 7.76 [7.65] 7.94 [7.88] 8.23 [6.42] 12 12 ts Events 0.40 [Weight () 95%-Cl (fixed) (ra ; 4.58] 0.0% ; 4.58] 0.0% ; 10.09] 0.7% ; 11.52] 0.8% ; 7.26] 11.6% ; 8.72] 27.2% ; 7.84] 59.7% ; 8.00] 100.0% ; 10.25] 1 Weigh 95%-Cl (fixed	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.6% 100.0% t Weight) (random) 6 33.1%
Heterogeneity: I ² = 100%, τ Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Weidenhammer 2008 their Fixed effect model Random effects model Heterogeneity: I ² = 98%, τ ² Overall risk for AE re Study Leung 2009	elated to acupuncto patients with AE tot 5 6 560 6942 19726 39078 = 0.0002, <i>p</i> < 0.01 elated to acupuncto treatments with AE tot	al patients 120	tients undergoing a tr Risk per 100 patients	reatment series Events 4.17 [1.34] 2.36 [0.84] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 8.61 [8.45] 7.76 [7.68] 8.23 [6.42] 12 12 ts Events 0.40 7.87	Weight V 95%-CI (fixed) (ra 1; 8.45] 0.0% ; 4.58] 0.0% ; 10.09] 0.7% ; 11.52] 0.8% ; 7.26] 11.6% ; 7.26] 11.6% ; 7.24] 59.7% ; 8.00] 100.0% ; 10.25] 1 Weigh 95%-CI (fixed [0.17; 0.72] 4.0% ; 7.42; 8.32] 27.6%	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.6% 100.0% t Weight) (random) 6 33.1% 6 33.4%
Heterogeneity: $l^2 = 100\%$, τ Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Weidenhammer 2008 their Fixed effect model Random effects model Heterogeneity: $l^2 = 98\%$, τ^2 D Overall risk for AE red Study Leung 2009 da Silva 2014	elated to acupunction patients with AE tot 5 6 560 6842 19726 39078 = 0.0002, p < 0.01 elated to acupunctor treatments with AE too 8 1092	aire among pa al patients 120 254 5998 6348 97733 229230 503397 843080 0 ure per treatments 2000 13884	tients undergoing a tr Risk per 100 patients	reatment series Events 4.17 [1.34] 2.36 [0.84] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 8.61 [8.45] 7.76 [7.68] 8.23 [6.42] 12 12 ts Events 0.40 7.87	Weight V 95%-Cl (fixed) (ra 8.45] 0.0% 3.4.58] 0.0% 3.10.09] 0.7% 11.52] 0.8% 4.7.26] 11.6% 3.8.72] 27.2% 3.7.84] 59.7% 4.7.84] 59.7% 4.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7% 5.7.84] 59.7	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.6% 100.0% t Weight) (random) 6 33.1% 6 33.4%
Heterogeneity: $I^2 = 100\%$, τ Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Weidenhammer 2008 their Fixed effect model Random effects model Heterogeneity: $I^2 = 98\%$, τ^2 O Overall risk for AE re Study Leung 2009 da Silva 2014 MacPherson 2001	elated to acupunction patients with AE tot 5 6 560 6842 19726 39078 = 0.0002, p < 0.01 elated to acupunctor treatments with AE too 8 1092	aire among pa al patients 120 254 5998 6348 97733 229230 503397 843080 0 ure per treatments 2000 13884 34407	tients undergoing a tr Risk per 100 patients	teatment series Events 4.17 [1.34] 2.36 [0.66] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 7.76 [7.65] 7.94 [7.88] 8.23 [6.42] 12 12 ts Events 0.40 [7.87] 15.05 [1	Weight M 95%-Cl (fixed) (ra 1; 8.45] 0.0% 5; 4.58] 0.0% 11.52] 0.8% 1; 7.26] 11.6% 0; 8.72] 27.2% 0; 7.84] 59.7% 10.25] 1 Weigh 95%-Cl (fixed 0.17; 0.72] 4.0% 7.42; 8.32] 27.6% 4.68; 15.43] 68.4%	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.6% (00.0% t Weight) (random) 6 33.1% 6 33.4% 6 33.4%
Heterogeneity: $l^2 = 100\%$, τ Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Weidenhammer 2008 their Fixed effect model Random effects model Heterogeneity: $l^2 = 98\%$, τ^2 D Overall risk for AE ref Study Leung 2009 da Silva 2014 MacPherson 2001 Fixed effect model	elated to acupunction patients with AE tot 5 6 560 6842 19726 39078 = 0.0002, p < 0.01 elated to acupunctor treatments with AE too 8 1092	aire among pa al patients 120 254 5998 6348 97733 229230 503397 843080 0 ure per treatments 2000 13884	tients undergoing a tr Risk per 100 patients	reatment series Events 4.17 [1.34] 2.36 [0.64] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 8.61 [8.45] 7.76 [7.68] 8.23 [6.42] 12 12 ts Events 0.40 [7.87] 15.05 [1 11.99 [1	Weight V 95%-Cl (fixed) (ra 1; 8,45] 0.0% ; 4,58] 0.0% ; 10.09] 0.7% ; 11.52] 0.8% ; 7.26] 11.6% ; 7.26] 11.6% ; 8.72] 27.2% 0; 7.84] 59.7% ; 8.00] 100.0% ; 10.25] 1 Weigh 95%-Cl (fixed [0.17; 0.72] 4.0% 7.42; 8.32] 27.6% 4.68; 15.43] 68.4%	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.5% 20.6% 100.0% t Weight) (random) 6 33.1% 6 33.4% 6 33.4%
Heterogeneity: I ² = 100%, τ Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Melchart 2004 Witt 2009 Weidenhammer 2008 then Fixed effect model Random effects model Heterogeneity: I ² = 98%, τ ² O Overall risk for AE re Study Leung 2009 da Silva 2014 MacPherson 2001 Fixed effect model Random effects model	elated to acupunctor patients with AE tot 5 6 560 6942 19726 39078 = 0.0002, p < 0.01 elated to acupunctor treatments with AE tor 8 1092 5179	aire among pa al patients 120 254 5998 6348 97733 229230 503397 843080 0 ure per treatments 2000 13884 34407	tients undergoing a tr Risk per 100 patients	reatment series Events 4.17 [1.34] 2.36 [0.64] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 8.61 [8.45] 7.76 [7.68] 8.23 [6.42] 12 12 ts Events 0.40 [7.87] 15.05 [1 11.99 [1	Weight M 95%-Cl (fixed) (ra 1; 8.45] 0.0% 5; 4.58] 0.0% 11.52] 0.8% 1; 7.26] 11.6% 0; 8.72] 27.2% 0; 7.84] 59.7% 10.25] 1 Weigh 95%-Cl (fixed 0.17; 0.72] 4.0% 7.42; 8.32] 27.6% 4.68; 15.43] 68.4%	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.6% (00.0% t Weight) (random) 6 33.1% 6 33.4% 6 33.4%
Heterogeneity: $l^2 = 100\%$, τ Study Wen 2016 Leung 2009 Weidenhammer 2008 pat. MacPherson 2004 Weidenhammer 2008 their Fixed effect model Random effects model Heterogeneity: $l^2 = 98\%$, τ^2 D Overall risk for AE ref Study Leung 2009 da Silva 2014 MacPherson 2001 Fixed effect model	elated to acupuncte patients with AE tot 5 6 560 6942 19726 39078 = 0.0002, p < 0.01	aire among pa al patients 120 254 5998 6348 97733 229230 503397 843080 0 ure per treatments 2000 13884 34407	tients undergoing a tr Risk per 100 patients	reatment series Events 4.17 [1.34] 2.36 [0.64] 9.34 [8.61] 10.74 [9.99] 7.10 [6.94] 8.61 [8.45] 7.76 [7.68] 8.23 [6.42] 12 12 ts Events 0.40 [7.87] 15.05 [1 11.99 [1	Weight V 95%-Cl (fixed) (ra 1; 8,45] 0.0% ; 4,58] 0.0% ; 10.09] 0.7% ; 11.52] 0.8% ; 7.26] 11.6% ; 7.26] 11.6% ; 8.72] 27.2% 0; 7.84] 59.7% ; 8.00] 100.0% ; 10.25] 1 Weigh 95%-Cl (fixed [0.17; 0.72] 4.0% 7.42; 8.32] 27.6% 4.68; 15.43] 68.4%	ndom) 1.7% 3.2% 16.8% 17.0% 20.3% 20.5% 20.5% 20.6% 100.0% t Weight) (random) 6 33.1% 6 33.4% 6 33.4%

Weight Weight 95%-Cl (fixed) (random)

0.0% 0.0% 0.1% 0.2% 0.2% 0.4% 0.5% 8.2% 16.1% 74.3%

0.4% 0.8% 1.2% 3.3% 5.1% 5.5% 9.5% 10.8% 20.5% 21.1% 21.6%

100.0%

Weight Weight 95%-CI (fixed) (random)

0.0% 0.0% 0.0% 0.1% 0.3% 0.3% 0.3% 0.4% 0.6% 7.1% 16.5% 74.2%

0.4% 0.5% 0.9% 3.5% 6.3% 6.5% 6.8% 7.4% 9.8% 17.2% 18.0% 18.4%

100.0%

0.2% 0.3% 0.5% 1.5% 2.7% 7.2% 37.3% 50.3%

100.0%

Weight Weight 95%-Cl (fixed) (random)

0.0% 0.0% 0.0% 0.2% 0.2% 0.3% 8.7% 90.6%

0.3% 0.3% 0.4% 0.6% 2.6% 5.4% 38.2% 49.5%

100.0%

0.00 [0.00; 79.82] 0.00 [0.00; 37.76] 0.00 [0.00; 24.54] 0.00 [0.00; 8.30] 0.00 [0.00; 4.40] 4.73 [0.89; 11.58] 0.61 [0.22; 1.20] 0.19 [0.11; 0.29]

0.23 [0.15; 0.34] 100.0% 0.45 [0.06; 1.18] --

0.00 [0.00; 666.31] 0.00 [0.00; 571.54] 0.00 [0.00; 480.11] 0.00 [0.00; 312.69] 0.00 [0.00; 69.17] 0.00 [0.00; 68.41] 99.35 [18.73; 243.56] 7.89 [2.84; 15.48]

7.89 [2.84; 15.48] 2.14 [1.24; 3.28] 2.57 [1.62; 3.74] 100.0% 5.45 [0.50; 15.67] --

0.00 [0.00; 79.82] 0.00 [0.00; 37.76] 0.00 [0.00; 24.54] 0.00 [0.00; 8.30] 0.00 [0.00; 4.88] 0.00 [0.00; 4.48] 0.00 [0.00; 4.40] 3.99 [0.38; 11.44] 4.73 [0.89; 11.58] 0.61 [0.22; 1.20] 2.36 [1.72; 3.10] 0.19 [0.11; 0.29]

0.43 [0.32; 0.56] 100.0% 1.01 [0.23; 2.33] --

0.00 [0.00; 666.31] 0.00 [0.00; 571.54] 0.00 [0.00; 480.11] 0.00 [0.00; 312.69]

 0.00
 [0.00; 312.69]

 0.00
 [0.00; 68.41]

 99.35
 [18.73; 243.56]

 0.00
 [0.00; 30.18]

 0.00
 [0.00; 27.91]

 0.00
 [0.00; 24.40]

 30.54
 [2.88; 87.54]

 7.89
 [2.84; 15.48]

 25.42
 [18.54; 33.39]

 2.14
 [1.24; 3.28]

4.75 [3.53; 6.14] 100.0% 7.98 [1.39; 20.00] --

ries Weight Weight 95%-Cl (fixed) (random)

0.0% 0.0% 0.1% 0.2% 0.6%

9.9% 89.1%

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7	A Overall SAE risk among patier	ts undergoing an acupuncture series	
-	Study patient	s with SAE total patients Risk per 10000	patients Events 95%-0
8	Wen 2016	0 120	→ 0.00 [0.00; 79.82
9	Leung 2009	0 254	→ 0.00 [0.00; 37.76
-	Yamashita 2000 da Silva 2014	0 391	→ 0.00 [0.00; 24.54 0.00 [0.00; 8.30
10	Zhao 2011	0 1968	0.00 [0.00; 4.88
11	Furuse 2017 Yamashita 1999	0 2180 2 5008	0.00 [0.00; 4.40 3.99 [0.38; 11.44
12	MacPherson 2004 Melchart 2004	3 6348 6 97733	4.73 [0.89; 11.58 0.61 [0.22; 1.20
· –	Endres 2004	45 190924	2.36 [1.72; 3.10
13	Weidenhammer 2008 ther.	17 882847	0.19 [0.11; 0.29
14	Fixed effect model	1188930 🗄	0.43 [0.32; 0.56
15	Random effects model Heterogeneity: $l^2 = 88\%$, $\tau^2 < 0.0001$,	<i>p</i> < 0.01	1.01 [0.23; 2.33
		0 2 4 6 8	10 12 14
16	B Overall SAE risk per acupuncte	<u>ire treatment</u>	
17	Study treatm	ents with SAE total treatments Risk per 1e	+06 treatments Events
18	Yamashita 2000	0 1441	→ 0.00 [0.0
	Wen 2016 Leung 2009	0 1680	→ 0.00 [0.0 → 0.00 [0.0
19	Park 2010	0 3071	→ 0.00 [0.0
20	da Silva 2014 Furuse 2017	0 13884	0.00 [0.0
21	MacPherson 2004	3 30196	> 99.35 [18.7
	White 2001 MacPherson 2001	0 31822	0.00 [0.0
22	Zhao 2011	0 39360	0.00 [0.0
23	Yamashita 1999 Melchart 2004	2 65482 6 760000	30.54 [2.8 7.89 [2.8
-	Endres 2004	45 1770000	25.42 [18.5
24	Weidenhammer 2008 ther.	17 7945000	2.14 [1.
25	Fixed effect model	10712382	4.75 [3.
26	Random effects model Heterogeneity: $l^2 = 85\%$, $\tau^2 < 0.0001$	<i>p</i> < 0.01	7.98 [1.3
		0 20 40 60	80 100 120 140
27	C Overall risk for SAE related t	o acupuncture among patients underg	oing a treatment series
28	Study patien	ts with SAE total patients Risk per 10000	patients Events 95%-
29	Wen 2016	0 120	→ 0.00 [0.00; 79.8
	Leung 2009 Yamashita 2000	0 254	→ 0.00 [0.00; 37.7 → 0.00 [0.00; 24.5
30	da Silva 2014	0 1157	0.00 [0.00; 8.3
31	Furuse 2017 MacPherson 2004	0 2180 3 6348	0.00 [0.00; 4.4 4.73 [0.89; 11.5
32	Melchart 2004	6 97733 -	0.61 [0.22; 1.2
	Weidenhammer 2008 ther.	17 882847	0.19 [0.11; 0.2
33	Fixed effect model	991030	0.23 [0.15; 0.3
34	Random effects model Heterogeneity: $I^2 = 41\%$, $\tau^2 < 0.0001$, p = 0.11	0.45 [0.06; 1.1
35	_		10 12 14
	D Overall risk for SAE related t		
36	Study treatm	ents with SAE total treatments Risk per 1e	+06 treatments Events
37	Yamashita 2000	0 1441	→ 0.00 [0.0
•.	Wen 2016 Leung 2009	0 1680	0.00 [0.0 0.00 [0.0
38	Park 2010 da Silva 2014	0 3071	- 0.00 [0.0 - 0.00 [0.0
39	Furuse 2017	0 14039	0.00 [0.0
40	MacPherson 2004 Melchart 2004	3 30196 6 760000 *-	→ 99.35 [18.7 7.89 [2.8
	Weidenhammer 2008 ther.	17 7945000	2.14 [1.
41	Fixed effect model	8771311	2.57 [1.
42	Random effects model	*	5.45 [0.5
43	Heterogeneity: $l^2 = 42\%$, $\tau^2 < 0.0001$	p = 0.09 0 20 40 60	80 100 120 140
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		185x257mm (281 x 2	281 DPI)
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3 4							
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б						Weight	Weight
7	Study	requiring treatment to		Risk per 1000 patients		(fixed)	(random)
8 9	Chung 2015 Wen 2016	1	59 120	·	→ 16.95 [0.01; 65.17 0.00 [0.00; 7.98 0.00 [0.00; 7.98	0.0%	10.8%
10	Leung 2009 Yamashita 2000 da Silva 2014	0 0 0	254	-	0.00 [0.00; 3.78 0.00 [0.00; 2.45 0.00 [0.00; 0.83	0.0%	
11	Melchart 2004 Witt 2009	6 4963	97733 = 229230		0.06 [0.02; 0.12 = 21.65 [21.06; 22.25	8.1%	13.9%
12	Weidenhammer 2008 acupuncturists	s 17	882847		0.02 [0.01; 0.03	72.9%	13.9%
13 14	Fixed effect model Random effects model		1211791		1.01 [0.95; 1.07 1.14 [0.00; 7.37		
15	Heterogeneity: $I^2 = 100\%$, $\tau^2 = 0.0073$,	p = 0	0	5 10 15 20			
16							
17							
18 19		286x8	2mm (18	0 x 180 DPI)			
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60	For peer review	v only - http://b	mjopen.b	mj.com/site/abo	out/guidelines	xhtml	

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Systematic review

1. * Review title.

Give the title of the review in English

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

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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.

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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

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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

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Petra

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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.**

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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, University 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

Granten funder of award number and the date of award

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.

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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.

International prospective register of systematic reviews

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 metaanalysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used. **BMJ** Open

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National Institute for Health Research

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 No) meta-analysis
Intervention No	
Meta-analysis No	
Methodology No	
Narrative synthesis No	
Network meta-analysis No	
Pre-clinical No	
Prevention No	
Prognostic No	
Prospective meta-analysis No	(PMA)
Review of reviews	

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NHS
National Institute for
Health Research

1 2	International prospective register of systematic reviews	Nationa Hea
3 4	No	
5 6 7	Service delivery No	
8 9	Synthesis of qualitative studies No	
10 11 12	Systematic review Yes	
13 14 15 16	Other No	
17 18 19 20	Health area of the review Alcohol/substance misuse/abuse No	
21 22 23	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	
24	Cancer	
25 26 27	No Cardiovascular No	
28 29	Care of the elderly No	
30 31 32	Child health No	
33 34	Complementary therapies Yes	
35 36 37	COVID-19 No	
38 39	Crime and justice No	
40 41	Dental No	
42 43 44	Dental No Digestive system No Ear, nose and throat	
45 46	Ear, nose and throat No	
47 48	Education No	
49 50 51	Endocrine and metabolic disorders No	
52 53	Eye disorders No	
54 55	General interest No	
56 57 58	Genetics No	
59 60	Health inequalities/health equity No	

Page 36 of 50

National Institute for Health Research

International prospective register of systematic reviews			
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2	International prospective register of systematic reviews
3	Infections and infestations
4	No
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6	International development
7	No
8	Mental health and behavioural conditions
9	No
10	Musculoskeletal
11	No
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13	Neurological
14	No
15	Nursing
16	No
17	Obstetrics and gynaecology
18	No Oral health No Palliative care No Perioperative care No Physiotherapy No Pregnancy and childbirth No
19	Oral health
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22	Palliative care
23	No
24	Perioperative care
25	No
26	Physiotherapy
27	No
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29	Pregnancy and childbirth
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31	Public health (including social determinants of health)
32	No
33	Rehabilitation
34	No
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36	Respiratory disorders No
37 38	
39	Service delivery
40	No
40 41	Skin disorders No Social care No
42	No
43	Social care
44	No
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46	Surgery
47	No
48	Tropical Medicine
49	No
50	Urological
51	No
52	Wounds, injuries and accidents
53	No
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55	Violence and abuse
56	No
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31. Language.

59 60

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

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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

Page 38 of 50

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PROSPERO International prospective register of systematic reviews

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.

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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	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

BMJ Open





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	6 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.				
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	dual 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.					
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 For peer review.only - http://bmjopen.bmj.com/site/about/guidelines.xhtml For more information, visit: <u>www.prisma-statement.org</u>. Page 2 of 2

Item No	Recommendation	Reported o Page No
Reporting o	f background should include	
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	page5 table
4	Type of exposure or intervention used	page5 table
5	Type of study designs used	page5 table
6	Study population	page5 table
Reporting o	f 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 o	f methods should include	1
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-
Reporting o	f 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 10-1 figures 3-5
		pages 10-1

MOOSE Checklist for Meta-analyses of Observational Studies

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Item No	Recommendation				
Reporting c	of discussion should include				
29	29 Quantitative assessment of bias (eg, publication bias)				
30	Justification for exclusion (eg, exclusion of non-English language citations)	page 16			
31	Assessment of quality of included studies				
Reporting c	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			

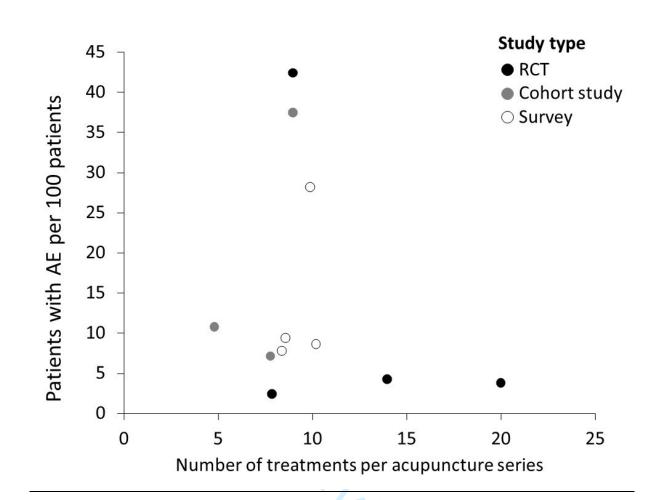
1	Bleeding		
2	Bleeding	 Small hemorrhage 	 Ecchymosis or hematoma
3	 Bleeding at needling site 	Lesion of blood vessel	accompanied by pain
4	 Mild / transient / minor bleeding 	Bruising	Ecchymosis or hematoma without
5	 Subcutaneous bleeding 	 Bruising at needling site 	pain
6	Hematoma	 Mild / transient bruising 	 Petechia or ecchymosis
7	Minor hematoma	Heavy bruising	,
	Subcutaneous / superficial hematoma	Subcutaneous bruise	
8	Local pain		
9	• Pain	• Pain upon insertion / stimulation	• Mild pain at the acupuncture site
10	Needle (-site) pain	Pain while needle was in place	more than one hour after treatment
11	 Pain where needle was inserted / at 	 Pain upon needle withdrawal at the 	 Pain disappearing after > 3 days
12	the site of the needle / in the	acupuncture point	• Chest pain (pneumothorax ruled out)
13	punctured region	 Pain after needle was removed 	• Electroacupuncture problems e.g. too
14	 Mild / transient pain at needling site 	Remaining / residual needle site pain	strong current resulting in pain
15	 Severe / strong / significant pain at 	 Prolonged / unacceptable pain at 	Local muscle pain
16	needling site	needle site	Unknown pain
17	Other local AE	needle site	
8	• Wheal	 Inflammation at application site 	• Significant rash on abdomen few days
19		Itch	after acupuncture
20	(Local) swelling Redness	 Itching and redness 	Cellulitis after treatment of
21	• Redness • Flare	_	edematous leg
22		 Itching in the punctured region Itching and erythema (suspected 	Edema in m. tibialis with anterior toe
	Localized erythema	 Itching and erythema (suspected contact dermatitis) 	lifting weakness (fully resolved)
23	 Needle-site / local skin reaction (Skin) irritation at asymptotic point 	Local allergic reaction (uticaria)	Other local AE (around the
24	 (Skin) irritation at acupuncture point 		acupuncture site)
25	Skin infection	Needle allergy	acupulicitale site
26	Local (skin) infection	 Allergic phenomena / reaction 	
27	Central nervous system		Distante de data e
28	• Aphasia	• Vertigo	Disturbed vision
29	• Dizziness	• Disorientation (length unspecified, 1	Spontaneous sensory perceptions
30	Mild / transient dizziness	h, 1 day)	• Shivering
31	• Imbalance	Severe disorientation	Seizure shortly after treatment
32	 Severe dizziness, vertigo or loss of 	Disturbed speech	• Tremor
33	balance	Slurred speech	
34	Peripheral nervous system		
35	Cold sensation at needling site	Prolonged deqi	 Hypaesthesia with numbness for three shows
36	 Feeling of acupuncture point at 	Strong acupuncture or heavy	three days
37	contralateral arm	sensation	• Insensibility
38	Paraesthesia	• Hypaesthesia	Itching, pins & needles, tingling or
	Temporary paraesthesia	Numbness	burning sensation
39 40	• Tingling	Numbness in upper extremity	Nerve irritation
40	 Tingling, prickling, burning, 	Numbness and unusual sensation	Neuritis
41	dysesthesia	 Severe stiffness or numbness 	
42	Aggravation of symptoms		
43	Aggravation	 Transient aggravation of symptoms 	Worsening of condition (after
44	 Aggravation of complaints / existing 	Aggravation of existing symptoms	removing needles)
45	ailment / existing symptoms	followed by improvement	Headache and or facial pain
46	Unexpected, severe or prolonged	 Deterioration / exacerbation of 	• pressure and or tension in the teeth
47	worsening of symptoms	symptoms	 Increased pain
48	Aggravation of symptoms during	General aggravation of symptoms	
49	acupuncture session / after treatment	 Worsening of health state 	
50	Vegetative nervous system		
51	 (Generalized) sweating 	Abnormal tiredness	 Significant / severe drowsiness
52	 Isolated sweating of hands 	 Severe / significant tiredness or 	 Drowsiness not causing hazard
53	Mild sweating	exhaustion	 Prolonged drowsiness (one day, one
54	 Flushed cheeks and body warmth 	• Lethargy	week)
- T		 Dazed 	 Drowsiness or restlessness
55	Hot flash		
	 Feeling of warm / heat / cold 	Vasovagal reaction: collapse,	 Orthostatic problems
56	 Feeling of warm / heat / cold Coldness / feeling cold 	dizziness, nausea & vomiting	Malaise
56 57	 Feeling of warm / heat / cold Coldness / feeling cold Freezing 	dizziness, nausea & vomiting Unconsciousness 	MalaisePoor concentration
56 57 58	 Feeling of warm / heat / cold Coldness / feeling cold 	dizziness, nausea & vomiting • Unconsciousness • Fainting	 Malaise Poor concentration Dry lips / mouth
56 57 58 59	 Feeling of warm / heat / cold Coldness / feeling cold Freezing 	dizziness, nausea & vomiting • Unconsciousness • Fainting • Faint / dizzy	 Malaise Poor concentration Dry lips / mouth Xerostomia
55 56 57 58 59 60	 Feeling of warm / heat / cold Coldness / feeling cold Freezing (Feeling of) fatigue 	dizziness, nausea & vomiting • Unconsciousness • Fainting	 Malaise Poor concentration Dry lips / mouth

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 	 Mild transient pain not at 	 Generalized muscle pain
at needling site	needling site	 Other / unspecified pain / aches
 Reactive pain at other body sites 	 Chest pain / tightness 	
Gastrointestinal / gynaecological system		
Nausea	 Tiredness next day after ten hours of 	 Increased peristalsis
 Mild and transient nausea 	diarrhoea (significant)	 Loss of appetite
 Severe nausea 	Stomach ache	 Other gastrointestinal complaints
• Vomiting	Abdominal distension	 Increased haemorrhage during
Severe vomiting	Impaired bowel function	menses
 Constipation 	Digestive problems	 Menstrual problems
Diarrhoea	 Entero- / gastrospasm 	
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 angeneration
Anxiety	• Discomfort	at practitioner
Anxiety and panic (up to one hour)	Restlessness or nervousness	• Fear
 Significant panic with sensation of 	 Disorientation, anxiety, nervousness, 	Grief / crying / tearful
heat and sweatiness	insomnia or emotional	Needle phobia, anxiety and rage
 Severe panic / agitation / depression 	Emotional /psychological reaction	• (Severe) nightmares
with anxiety	(Uncontrolled) euphoria Cignificant emotional release (manie	 Other mood swings
Depressed emotional state or neurovogotativo dvctonia	 Significant emotional release (manic, releved, rage or confusion) 	
neurovegetative dystonia	relaxed, rage or confusion)	
Sleeping problems	• Covera cleaning problems	
Sleep disturbances Impaired sleep	Severe sleeping problems Severe sleeping problems	• Insomnia
Impaired sleep Mova caused adverse events	Severe sleeplessness	
Moxa caused adverse events	• Burns	• Blister following moxibustion
Burn injury	• Burns	
 Needling malpractice Left alone / unattended in the 	Eailure to remove peodle/s)	
• Left alone / unattended in the treatment room for too long	 Failure to remove needle(s) Forgotten / dropped needle 	
Broken needle	Needle lost or forgotten	
Stuck or bent needle	- Meetie lost of lorgotten	
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)
• Fever	Concomitant diseases of recent	adverse events
Angina	appearance	 other negative reactions
Eye irritation	Change of taste	Unknown due to incomplete record
	 Change of weight / weight reduction 	form

n 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 (<i>direct quotes</i> 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 2 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 hospite 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/um 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 Reportto 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 neede treatment, received from the study office an additional, more detailed standardised questionnair 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 ir the TCT Clinic But 2 cases identified from reports tha 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 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

Page 48	of 50
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Study	Total number of patients	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] 0.05	0.24 [0.00; 0.96]	6.36 [4.20; 8.92]	0.98 [0.26; 2.16]	6.11 [4.00; 8.64] 0.05	4.89 [3.01; 7.19]		1.96 [0.84; 3.52] 0.05	17.85 [14.29; 21.7(
Zhao 2011	1968	3.40 [2.65; 4.25] 12.80	[0.00; 0.20] 6.24		0.10 [0.01; 0.29]	1.06	[0.00; 0.20]			[0.00; 0.20]	1.10
Furuse 2017	2180	[11.43; 14.23]	[5.26; 7.29]			[0.67; 1.53]					[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]
tau²		0.0008	0.0085	0.0494	0.0012	0.0017	0.0018	0.0004	0.0005	0.0008	0.0003
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

Page 49 of 50

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tudy	Total number					s with AE per 100	putterite [55% et]			
	of patients	Headache	Cardiovascular system	Motor system	Generalized skin reaction	Needling malpractice	Emotional interference	Sleeping problems	Moxibustion AE	Respiratory system
ist 1992	29			41,38				20,69		
		13.56		[24,41; 59,48]	1,69	0,00		[8,19; 37,03]		
hung 2015	59	[6.0980; 23.38]			[0,00; 6,52]	[0,00; 1,62]				
Ven 2016	120	[[-,, -,]	[-,, _,]				
ven 2010	120									
lelchart 1998	121		0.83 [0.00; 3.21]				0,83 [0,00; 3,21]			
			[0.00; 3.21]				[0,00; 3,21]			
eung 2009	254									
amashita 2000	391	0.51								
2000	551	[0.0485; 1.46]	0.10				0.00			0.04
rnst 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]
	1050	[0.0403, 1.40]	[0.05, 1.40]	0,10			[0,20, 2,10]			[0,00, 0,00]
hao 2011	1968			[0,01; 0,29]						
uruse 2017	2180	0.05				0,60			0,96	
		[0.0000; 0.18] 1.37	0.60	0.25		[0,32; 0,96]		0,13	[0,60; 1,42]	0.07
Veidenhammer 008 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]
lacPherson	6240	1.21	[0.12, 0.01]	[0,22, 0,32]		1,04	1,24	0,74	0,44	[0,02, 0,10]
004	6348	[0.9585; 1.50]				[0,81; 1,30]	[0,99; 1,53]	[0,54; 0,97]	[0,29; 0,62]	
lelchart 2004	97733	0.04				0,25				
		[0.0275; 0.05]				[0,22; 0,28] 0,00	0,04	0,04	0,00	
ndres 2004	190924					[0,00; 0,00]	[0,03; 0,05]	[0,03; 0,05]	[0,00; 0,00]	
Vitt 2009	229230	0.52	0.27	0,08	0,09	0,01	0,09	0,04	0,01	0,02
	223230	[0.4944; 0.55]	[0.25; 0.29]	[0,07; 0,09]	[0,08; 0,10]	[0,00; 0,01]	[0,08; 0,11]	[0,03; 0,05]	[0,00; 0,01]	[0,01; 0,02]
Veidenhammer	503397	0.03 [0.0287; 0.04]	0.42			0,28 [0,27; 0,30]	, 0,0197 [0,02; 0,02]			
008 therapists		0.12	[0.40; 0.43]	0,09	0,09	0,11	0,04	0,05	0,00	0,02
ixed effect		[0.11; 0.13]		[0,08; 0,10]	[0,08; 0,10]	[0,11; 0,12]	[0,04; 0,04]	[0,04; 0,05]	[0,00; 0,01]	[0,01; 0,02]
andom effect		0.51	0.40	0,38	0,35	0,22	0,20	0,16	0,14	0,04
andomenect		[0.03; 1.55]	[0.24; 0.61]	[0,00; 4,79]	[0,00; 35,67]	[0,01; 0,67]	[0,00; 0,81]	[0,00; 0,91]	[0,00; 1,16]	[0,00; 0,26]
au²		0.0012	0.0001	0.0011	0.0029	0.0009	0.0002	0.0001	0.0002	0.0001
		99.6%	96.4%	94.6%	= 58.2%	99.7%	98.7%	97.1%	98.3%	69.0%
		[99.6%; 99.7%]	[93.9%; 97.9%]	[90.2%; 97.1%]	[0.0%; 90.1%]			[95.3%; 98.2%]	[97.3%; 99.0%]	[0.0%; 91.0%]
-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

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Study	Total number of treatments	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]	[0.03, 1.72]	0.01	0.11 [0.06; 0.17]	[0.00, 0.27]	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]
tau²		0.0169	0.0095	0.0004	0.0213	0.0055	0.0011	0.0008	0.0085	0.0008	0.0025
l 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

Page 51 of 50

35 36

44 45 46

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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
'amashita 2000	1441	0.14 [0.01; 0.40]				0.62 [0.28; 1.10]				
laSilva2014	13884					0.24 [0.16; 0.33]				
/lelchart1998	1200		0.08 [0.00; 0.33]				0.08 [0.00; 0.33]			
/lacPherson2005	9408						0.67 [0.51; 0.84]			
uruse2017	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]	
rnst2003	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]			
'amashita 1999	65482					0.04 [0.03; 0.06]	0.01 [0.00; 0.02]		0.01 [0.00; 0.02]	
ark2009	1095									
eung2009	2000									
ark2010	3071	0.03 [0.00; 0.13]		0.10 [0.02; 0.24]		0.10 [0.02; 0.24]				
Vhite2001	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]	
AacPherson2001	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]	
ixed 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]	
andom 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]
au²		0.0002	0.0001	0.0001		0.0002	0.0004		0.0001	
2		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%]	
-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