Manual Therapy 15 (2010) 355–363

Contents lists available at ScienceDirect

Manual Therapy

journal homepage: www.elsevier.com/math

Systematic review

Adverse events and manual therapy: A systematic review

Dawn Carnes [a,*], Thomas S. Mars [b], Brenda Mullinger [b], Robert Froud [a], Martin Underwood [c]

[a] Barts and The London School of Medicine and Dentistry, Centre for Health Sciences, 2 Newark St, London E1 2AT, UK
[b] European School of Osteopathy, Boxley House, Boxley, Maidastone, Kent ME14 3DZ, UK
[c] Warwick Medical School, Gibbetts Hill, Coventry, CV4 7AL, UK

ARTICLE INFO

Article history:
Received 11 August 2009
Received in revised form
9 December 2009
Accepted 17 December 2009

Keywords:
Systematic review
Adverse events
Manual therapy

ABSTRACT

Objective: To explore the incidence and risk of adverse events with manual therapies.
Method: The main health electronic databases, plus those specific to allied medicine and manual therapy, were searched. Our inclusion criteria were: manual therapies only; administered by regulated therapists; a clearly described intervention; adverse events reported. We performed a meta-analysis using incident estimates of proportions and random effects models.
Results: Eight prospective cohort studies and 31 manual therapy RCTs were accepted. The incidence estimate of proportions for minor or moderate transient adverse events after manual therapy was ~41% (CI 95% 17–68%) in the cohort studies and 22% (CI 95% 11.1–36.2%) in the RCTs; for major adverse events ~0.13%. The pooled relative risk (RR) for experiencing adverse events with exercise, or with sham/passive/control interventions compared to manual therapy was similar, but for drug therapies greater (RR 0.05, CI 95% 0.01–0.20) and less with usual care (RR 1.91, CI 95% 1.39–2.64).
Conclusions: The risk of major adverse events with manual therapy is low, but around half manual therapy patients may experience minor to moderate adverse events after treatment. The relative risk of adverse events appears greater with drug therapy but less with usual care.

Manual therapies are widely used particularly to treat spinal disorders. Manual therapy interventions range from advice, through soft tissue massage and passive or active mobilisation, to manipulations (high velocity thrust techniques taking joints beyond their usual range of motion (Evans and Breen, 2006)). International treatment guidelines support the use of manual therapy for some musculoskeletal disorders (Airaksinen et al., 2004; NICE Guidelines, 2009) but there are concerns about potential risks particularly with manipulation of the cervical spine (Ernst, 2002). Adverse events from manual therapy range from the catastrophic, such as cervical artery dissection producing a stroke, through bruising, to muscle soreness that could be regarded as a minor, and expected, consequence of treatment. An understanding of the comparative incidences of adverse events of different severities is needed to inform patient choice about manual therapy. We report here a systematic review of published prospective studies of manual therapy to determine the incidence of adverse events of different severity and relative risk of different therapies.

1. Method

1.1. Definitions

We defined manual therapy as: any techniques administered manually, using touch, by a trained practitioner for therapeutic purposes. Throughout our research, depending on the author descriptions, we used the following classification terms for adverse events (Carnes et al., 2010).

- `Major': medium to long term; moderate or severe intensity
- `Moderate': medium to long term; moderate intensity
- `Minor': short term and mild intensity

1.2. Searches and selection

We searched Medline (using OVID), Science Direct, Web of Science, PEDro (Physiotherapy Evidence Database) Index of Chiropractic literature, Cambridge Journals, AMED (Allied and Alternative Medicine Database) and JAMA (Journals American Medical Association) from inception to March 2008 using the following terms and derivatives of them customised for each search engine: (*chiropractic*, *osteopathy*, *orthopaedic*, *physiotherapy*, *manual*

* Corresponding author. Tel.: +44 20 7882 2546.
E-mail address: d.carnes@qmul.ac.uk (D. Carnes).

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doi:10.1016/j.math.2009.12.006

therapist, *manipulation*, *cavitation*, *mobilisation*, *articulation*, *adjustment*) *AND* (*adverse event*, *effect*, *reaction*, *outcome*, *complication*, *response*, *side effects*, *spine*, *vertebra*, *muscle*, *disc*, *body*, *vascular*, *neurological*). In addition we tracked citations from articles.

Our inclusion criteria were: randomised controlled trials (RCTs) and prospective cohort studies that contained original data about adverse events from manual therapy delivered by statutory registered professional(s) or a regulated professional(s) in a manual therapy; the intervention or therapy involved physical and/or manual contact with an individual with therapeutic intent, administered without the use of mechanical, automated, electronic, computer or pharmacological aides/products; patients were conscious during the intervention. We excluded mixed and multidisciplinary interventions where the manual therapy effects would be unclear/undeterminable, and self-administered interventions, including exercise programmes

Two reviewers (DC and TM) searched the databases and selected relevant articles independently. A third party (MU) acted as an arbitrator in cases of uncertainty. The inclusion and exclusion criteria were applied at each stage of the review selection process. At the abstract selection stage we separated the database into RCT and non-RCT manual therapy and adverse event articles. Due to poor reporting of adverse events, especially in the older manual therapy efficacy trials, we decided to review and extract data from RCTs published after the publication of the CONSORT statement (Altman, 1996). The CONSORT group recommended minimum standards for RCT reporting (http://www.consort-statement.org), this included publishing data on adverse events in trials.

1.3. Quality assessment

We used a modified CASP quality appraisal template for the cohort studies (http://www.phru.nhs.uk/Pages/PHD/resources.htm (accessed 4.4.09)). This comprised of 15 different methodological questions, the criteria assessed ranged from generic, for example, was the aim clearly stated?, to specific, for example, was temporality/causation considered? We used a modified musculoskeletal appraisal template for the RCTs (Koes et al., 1995). This is a weighted appraisal system using 17 quality criteria. Each criterion is allocated points depending on importance. Criteria assessed are: the study population, the intervention, the effect and data presentation and analysis. Scores are appointed accordingly and a composite score out of 100 given. The quality assessment enabled us to grade studies from high to low; studies in the upper quartile range of quality scores were classified as high those in the mid-upper range were classified as medium; studies in the two lower quartiles (i.e. below half of the appropriate quality criteria were not satisfied) were low quality. A sample of papers (10%), were jointly reviewed to check the quality appraisal process: only minor disagreements occurred with some of the weighted scores, and these were not sufficient to unduly affect the final classification categories.

1.4. Statistical analysis

1.4.1. Prospective cohort studies

We extracted data from the cohort studies on subjects with minor, moderate, or major adverse events. Using a random effects model, we meta-analysed data estimating the incidence of minor/moderate or major adverse events.

1.4.2. Randomised controlled trials

Firstly, we used all data from the manual therapy arms of selected RCTs to estimate the incidence of minor, moderate or major adverse events using a random effects model in a similar manner to that used for the cohort studies. Secondly, we fitted random effects models to determine the relative risk (RR) of adverse events from manual therapy compared with: exercise, drug therapy, usual general practitioner or medical care, sham, passive or control interventions. Where no adverse events were observed, we estimated the upper half of 95% confidence interval (CI) using the Exact method (Clopper and Pearson, 1934).

2. Results

There were 230 RCT articles selected for full paper review. Our searches identified 60 non-RCT articles and 36 articles on RCTs that fulfilled our inclusion criteria (Fig. 1). To maximise the quality of evidence reviewed we focused our analyses on prospective cohort studies and RCTs only. We report here data from eight prospective cohort studies (nine articles, Table 1) and 31 RCTs (five articles presented data from the same trials, Table 2). The remaining articles consisted of reviews of literature, questionnaire surveys, quasi-experimental and before and after studies. No deaths, cerebrovascular accidents or stroke were reported in any of the prospective cohort studies or RCTs.

2.1. Prospective cohort studies

Eight prospective cohort studies were specifically designed to investigate adverse events with manual therapy. These studies represented at least 36,949 manual therapy treatments that included manipulation in 22,898 patients (Table 1).

2.1.1. Major adverse events

Of the eight studies, one (Thiel et al., 2007) reported 14 cases of `unbearably severe side effects' in 4712 treatments (0.13%). Thiel et al. (2007) reported an upper risk rate for `serious adverse events' using Hanley's `rule of three' (Hanley and Lippman-Hand, 1983) of approximately 0.01% (3/28,109 consultations). Combining all the data from the cohort studies (Table 1) we estimated, an upper 95% CI incidence risk rate of major adverse events (as per our definition) of 0.007% (0/42,451) after treatment or 0.01% (0/22,833) per patient.

2.1.2. Minor and moderate adverse events

The pooled proportion estimate of incidence of minor or moderate adverse events in patients or after treatment consultations (some patients may have had more than one treatment) was ~41% (95% CI 17–68%).

The majority of minor or moderate adverse events reported by patients occurred within 24 h of treatment (53% (Barrett and Breen, 2000), 58% (Leboeuf-Yde et al., 1997), 87% (Senstad et al., 1996b)) and most resolved within 48 h (64% (Cagnie et al., 2004), 74% (Leboeuf-Yde et al., 1997), 94% (Senstad et al., 1996b)). Rubinstein et al. (2007) reported that 72% of adverse events occurred after the first treatment.

2.2. Randomised controlled trials

We identified 36 papers detailing adverse event data from 31 RCTs, which together represented 5060 participants (Table 2). One hundred and eleven trial papers did not explicitly report any adverse event data; these were excluded from our analyses (Fig. 1).

2.2.1. Major adverse events

There were no reports of any major adverse events in any trial. The 31 RCTs included 2281 participants who received manual therapy and 2779 who received other therapies. Fifteen trials reported that no adverse events occurred regardless of the intervention administered. We estimated an upper incidence rate of

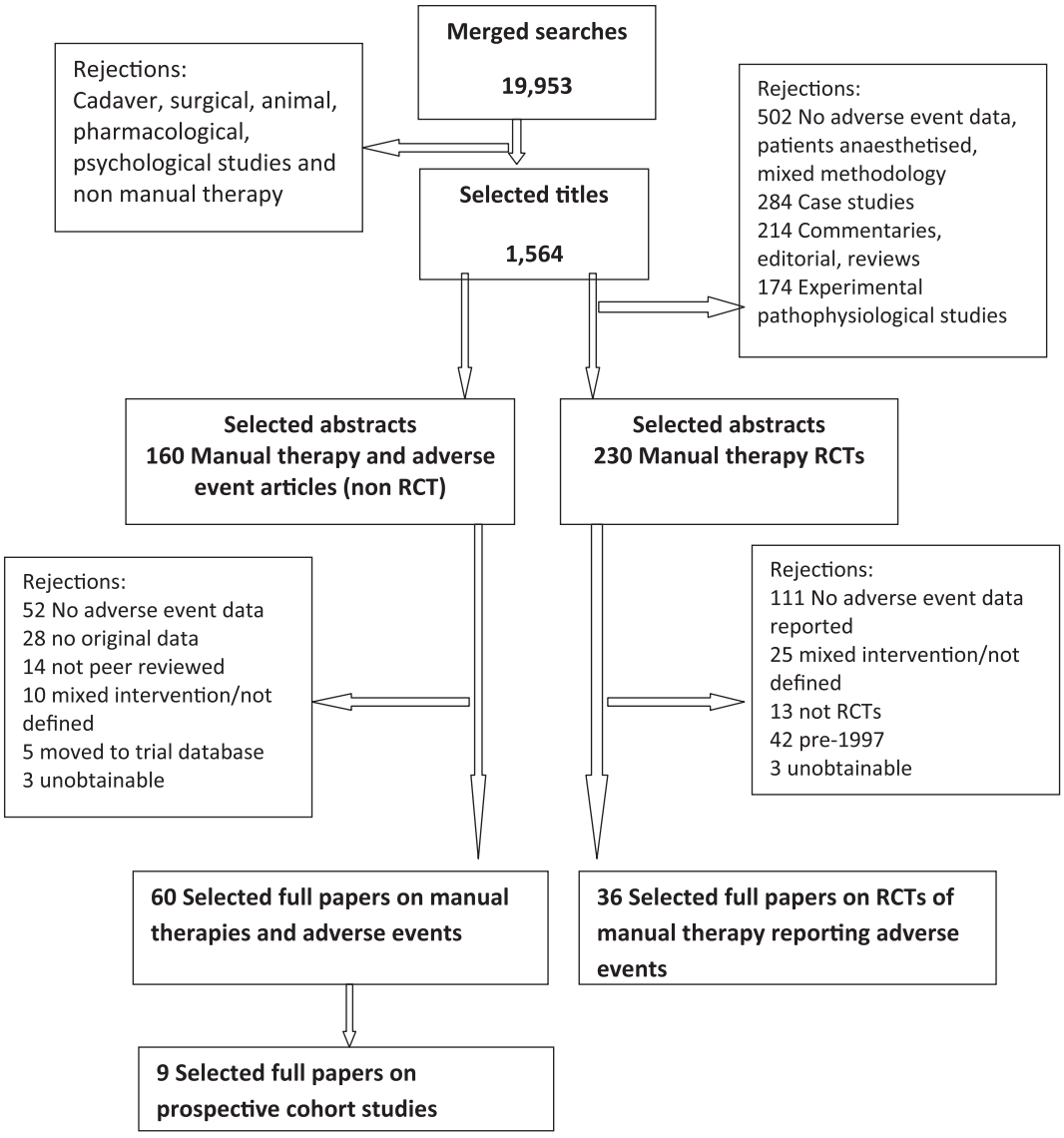

Fig. 1. Flow chart of review.

major adverse events of ~0.13% (0/2301) after manual therapy treatment.

2.2.2. Mild and moderate adverse events

The pooled estimate of incidence of recorded minor or moderate adverse events in the manual therapy arms of the RCTs was 22% (95% CI 11.1–36.2%). Meta-analyses of data comparing manual therapy with other interventions are shown in Figs. 2 and 3 (Plots A–D, Plot A exercise vs manual therapy, Plot B medication vs manual therapy, Plot C general practitioner/usual care vs manual therapy and Plot D sham/passive and control interventions vs manual therapy). Manual therapy interventions, which predominately included manipulation, produced more adverse events than general practitioner care (RR, 1.91, CI 95% 1.39–2.64); about the same number as exercise (RR 1.04, CI 95% 0.83–1.31), and fewer than drug therapy (RR 0.05 CI 95% 0.0–0.20). There was a non-significant trend for manual therapy to produce more adverse events than sham, passive or control interventions (RR 1.84 (CI 95% 0.93–3.62), Fig. 3).

An I^2 value of 0% indicates absence of heterogeneity between pooled studies, larger values indicate increasing heterogeneity (Higgins et al., 2003). The I^2 statistic in plots A–D shows low statistical heterogeneity, additionally, clinical homogeneity was good and therefore pooling of data was appropriate (Higgins et al., 2003). All studies included manual therapy which included, or could include, manipulation. The exercise interventions arms were similar. The medication arm comparisons were NSAIDs and amitriptyline (Nelson et al., 1998). In a sensitivity analysis, excluding Nelson et al. the pooled data indicated the risk of taking medication was still greater than manual therapy. In the two studies comparing GP and usual care, the `interventions' were matched with usual care plus best practice advice. The sham and passive controls whilst varied did not include manipulation.

3. Discussion

This systematic review of published RCTs and cohort studies confirms that, in line with the reports of others (Senstad et al., 1996a,b; Leboeuf-Yde et al., 1997; Barrett and Breen, 2000; Cagnie et al., 2004; Rubinstein et al., 2007), around half of people treated with manual therapy can expect minor to moderate adverse events after treatment, especially after the first treatment (Rubinstein

Table 1
Prospective cohort studies of adverse events in manual therapy.

Author	Quality rating	Manual therapists (country of origin)	Treatments	Patients	Adverse events
Barrett and Breen (2000)	High	Chiropractic (UK)	80	80	53% (42) of patients some sort of adverse events over two days (mild/moderate) 0 major events
Cagnie et al. (2004)	High	Chiropractors, Physical therapists, Osteopaths (Belgium)	465	465	60.9% (283) patients reported at least one adverse event, 0 major adverse events
Garner et al. (2007)	Medium	Chiropractic (Canada)	1968	259	0% (0/259) adverse events reported or observed
Leboeuf-Yde et al. (1997)	Medium	Chiropractic (Sweden)	1858	625	44% (275) of patients reported at least one adverse event during the course of treatment, 0 major incidents reported
Rubinstein et al. (2007)	High	Chiropractors (Netherlands)	4891	529	46% (243) of patients reported at least adverse event after their first treatment, 56% (296) of patients reported at least adverse event after any of three treatments, 0 `serious neurological complaints', 1% (5) reported being worse at 12 months after treatment
Senstad et al. (1996b)	High	Chiropractors (Norway)	368	95	34% (125) of treatments resulted in reports of adverse events, 0 `alarming' adverse events reported
Senstad et al. (1996a)	High	Chiropractors (Norway)	4712	1058	55% (581) of patients reported at least one adverse event throughout the course of treatment, 0.1% or 12 patients reported `unbearably severe side effects'
Thiel et al. (2007)	High	Chiropractors (UK)	28,109	19,722	0 `significant adverse events' occurred immediately after treatment, 1.3–1.6 (448) moderate adverse events occurred after cervical spine treatment, approx 4% (1124) headaches occurred after cervical spine treatments
Total			42,451	22,833	

et al., 2007). However, the incidence of major adverse effects is small; there were no reports of a catastrophic adverse event such as death or stroke. Importantly, our study provides the first pooling of data from randomised controlled trials of manual therapy on the incidence of adverse events. Our analysis shows that the relative risk of minor or moderate adverse events was similar for manual therapy and exercise treatments, and for sham/passive/control interventions. Also, in comparison with manual therapy, the risk of having an adverse event was greater with drug therapy but less with general practitioner/usual care.

3.1. Methodological issues

We found an approximate two-fold difference in the rates of reported mild or moderate adverse events between the prospective cohort studies and the manual therapy arms of randomised controlled trials (41% vs 22% respectively). As the cohort studies were specifically designed to identify adverse events, they might be expected to give a more accurate assessment, so this finding suggests under-reporting of adverse events in RCTs. Typically, the RCTs provided poor descriptions and definitions of adverse events as they were not the primary outcome measure. Additionally, strict trial recruitment protocols generally dictate participants have few risk factors, thereby contributing to a lower reported incidence of adverse events. However, as long as there was no systematic reporting bias between the arms within each trial, we have a reasonable estimate of the relative risk from manual therapy.

Manual therapy has not been subjected to the same scrutiny and surveillance as pharmacological interventions and there is no equivalent to post-marketing surveillance as used in the pharmaceutical industry. There are methodological difficulties when collecting and reporting manual therapy adverse event data (Ernst, 2001; Stevinson et al., 2001; Kerry et al., 2008). Unclear definitions, the variety of manual therapies, different time periods over which data are collected, whether the patient or the practitioner reports the adverse event, and varying data collection methods (free response or tick list choice) all affect analysis and outcome. Additionally, issues of confidentiality, patient satisfaction, and loss of patients at follow-up can all influence true incidence figures in observational studies (Thiel and Bolton, 2006; Thiel et al., 2007). Reporting bias by both patients and practitioners, patient selection bias, and patients who may be treated concurrently by other health professionals and may well self-medicate further affect findings, and strict adherence to protocols can be difficult (Thiel et al., 2007).

We detected similar risks of adverse events occurring for manual therapy and for exercise. Although our data showed manual therapy produced more adverse events than sham, passive and control interventions this was not statistically significant. This finding needs to be set against the evidence of effectiveness for manual therapies in the treatment of low back pain (NICE Guidelines, 2009), a condition for which medication is often prescribed. Four RCTs compared manual therapy with either NSAIDs (any) (Giles et al., 1999, 2003), diclofenac (Hancock et al., 2007), or amitriptyline (Nelson et al., 1998). Our meta-analysis showed that the relative risk of having minor or moderate adverse event with manual therapy (high velocity thrust) was significantly less than the risk of taking the medication. Others have estimated the risk of death from using NSAIDs for osteoarthritis to be 100–400 times the risk of death from cervical manipulation (Dabbs and Lauretti, 1995). It has been estimated that lumbar manipulation is 37,000–148,000 times safer than NSAIDs and 55,500–444,000 times safer than surgery for the treatment of lumbar disc herniation (Oliphant, 2004). Cauda equina syndrome has been calculated to be 7400–37,000 times more likely to occur as a complication of surgery than from spinal manipulation (Oliphant, 2004).

We estimated the upper 95% confidence interval for risk of a major adverse event as ~0.003%, using the Exact method (according to binomial theory); other studies have used Hanley's rule of three (Hanley and Lippman-Hand, 1983). Hanley explained that where no adverse event had been observed one cannot assume there is no risk simply because none occurred. He suggested that if no patients (n) show an adverse event, then the upper 95%

Table 2
RCTs reporting adverse events.

Author	Quality rating	Interventions	MT	*n*	Exercise	*n*	Drug	*n*	GP/usual care	*n*	Sham passive control	*n*
Bove et al. (1998)	Low	Soft tissue and SM (37) vs soft tissue and placebo laser (control) (38)	0	37							0	38
Bronfort et al. (2001)	Med.	SM and low technology exercise (63) vs MedX exercise (60) vs spinal manipulation (64)	16	127	9	60						
Burton et al. (2000)	Med.	SM (20) vs chemonucleolysis (20) (single injection of chymopapain)	0	20					0	20		
Cherkin et al. (2001)	Med.	Acupuncture (94) vs massage (78) vs self care education (90)	10	78							0	90
Cleland et al. (2007)	Med.	Nonthrust mobilisation/SM (30) vs thrust mobilisation/SM (30)	10	30								
Evans et al. (2003) (22)	Med.	Chiropractic care (10) vs medical care (9) vs self care education (9)	9	10					5	9	3	9
Ferreira et al. (2007)	High	General exercise (80) vs motor control exercise (80) vs SM (80)	0	80	0	160						
Giles et al. (1999)	Med.	Needle acupuncture (20) vs NSAID medication (21) vs chiropractic spinal manipulation (36)	0	36			3	21				
Giles et al. (2003) (25)	Med.	Needle acupuncture (34) vs NSAID medication (40) vs chiropractic SM (35)	0	35			7	40				
Haas et al. (2004)	Med.	3 visits (8) vs, 9 visits (8) vs 12 visits (8)	0	24								
Hancock et al. (2007)	Med.	SM + diclofenac (60) vs placebo SM diclofenac (60) vs SM and placebo diclofenac (59) vs placebo SM and placebo diclofenac (60)	0	120			0	119				
Hawk et al. (2005)	High	Chiropractic SM and trigger point therapy (54) vs sham SM and effleurage (57)	1	54							0	57
Hawk et al. (2006)	Med.	Chiropractic SM (41) vs non SM mindbody approach (40)	0	41							0	40
Hay et al. (2005)	Med.	Brief pain management programme (201) vs manual physiotherapy (201)	0	201							0	201
Hoeksma et al. (2004)	Med.	Manual therapy (56) vs exercise therapy (53)	0	56	2	53						
Hondras et al. (1999)	Med.	SM therapy (69) vs low force mimic manoeuvre (69)	2	69							3	69
Hoving et al. (2002, 2006)	High	Manual therapy (60) vs exercise therapy (59) vs GP care (64)	42	60	39	59			22	64		
Hsieh et al. (2002)	Med.	Backschool programme (48) vs myofascial therapy programme (51) vs joint manipulation (49) vs combined joint manipulation and myofascial therapy (52)	13	101							6	48
Hurwitz et al. (2002,2006)	Med.	Medical care (170) vs medical care + physical therapy (170) vs chiropractic care (169) vs chiropractic care and physical modalities (172)	0	169	0	342			0	170		
Hurwitz et al. (2004, 2005)	Med.	SM with and without heat and with and without EMS (171) vs mobilisation with and without heat and with and without EMS (165)	48	171								
Jull et al. (2002)	Med.	SM (51) vs SM plus exercise (49) vs therapeutic exercise (52) vs control (48)	0	100	0	52					0	48
Nelson et al. (1998)	High	SM (77) vs amitriptyline (70) vs combined (71)	0	77			47	141				
Plaugher et al. (2002)	Med.	Chiropractic adjustment (9) vs brief massage (8) vs control (6)	0	17	0	6						
Santilli et al. (2006)	Med.	SM (53) vs simulated SM (49)	0	53	0	49						
Sawyer et al. (1999)	Med.	Chiropractic SM (9) vs sham SM (11)	0	20	0	11						
Skargren et al. (1997,1998)	Med.	Chiropractic (179) vs physiotherapeutic care (144)	0	144								
Strunk and Hondras (2008)	Low	Cervical SM (3) vs combined SM and muscle energy technique (3)	2	6								
Tuchin et al. (2000)	Low	Cervical SM therapy (83) vs control (detuned interferential (40)	2	83							0	40
UK BEAM team (2004)	High	General practice (338) vs exercise (310) vs SM (353) vs SM and exercise (333)	0	353	0	310			0	338		
Vicenzino et al. (2001)	Low	Lateral glide mobilisation (8) vs placebo (8) vs control (8)	0	8							0	16
Williams et al. (2003)	Med.	Usual GP care (109) vs GP care and additional 3 sessions of Osteopathic SM (92)	0	92					0	109		
		Totals	107	2301	50	781	57	321	27	372	12	656

MT = manual therapy, SM = spinal manipulation.

confidence limit for the risk may be estimated as $3/n$. Using this method, Thiel et al. (2007) estimated the upper 95% confidence limit of risk for serious adverse events following chiropractic care as ~0.01%. Both methods produced data that indicated the risk of major adverse events is low.

Despite our initial search identifying many published articles, editorials, letters and case studies ($n = 498$) reporting the risk of strokes or cervical artery dissections specifically from cervical manipulation, none were reported in any of the studies we reviewed. However, cohort studies and randomised controlled trials are not the best research method for estimating the frequency of very rare events.

To give a perspective of risk, regardless of care, ~208 adults per 100,000 in the general population may suffer a stroke (Cashley et al., 2008). The background incidence of stroke, based on patient

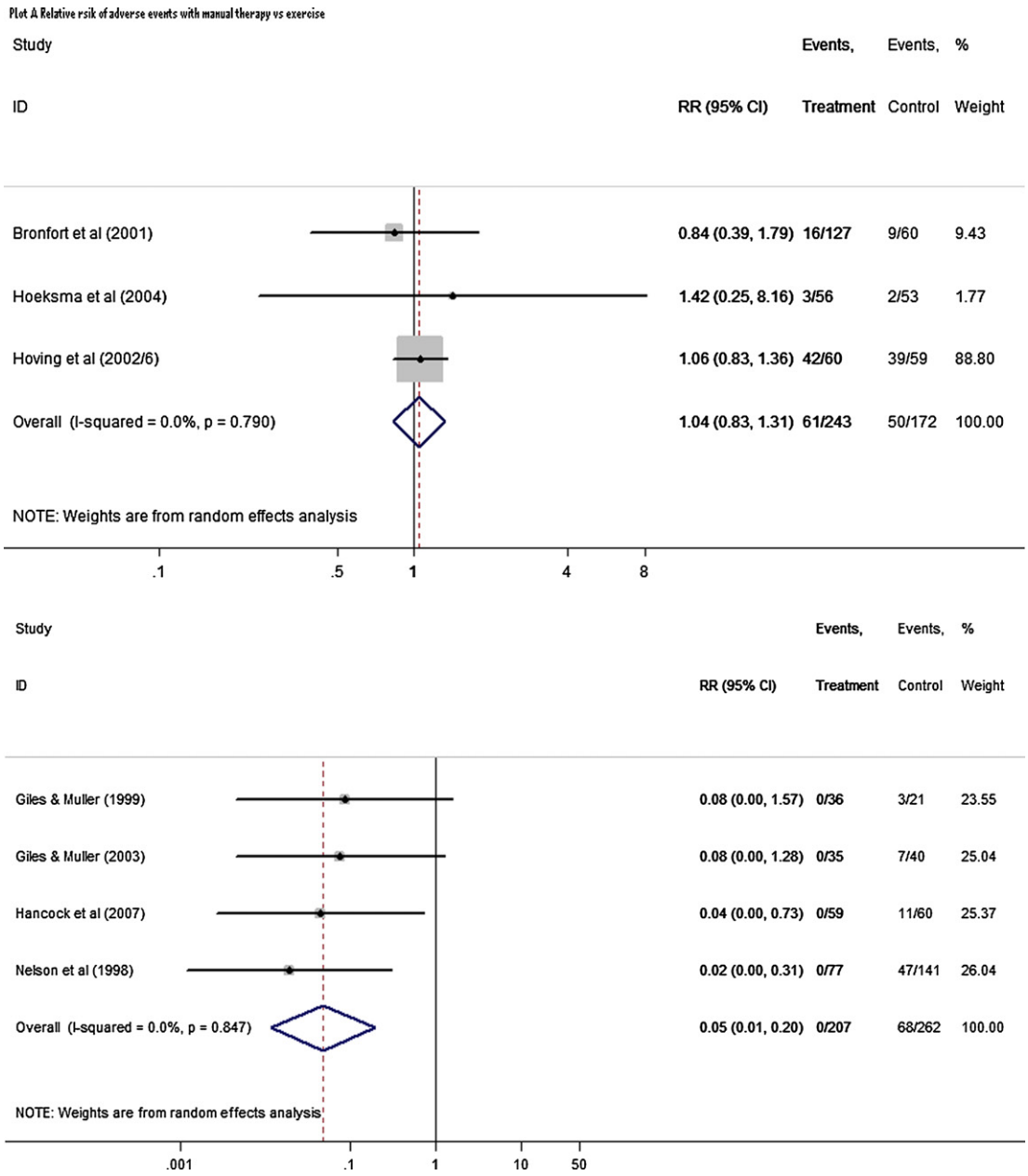

Fig. 2. Plot A (first) manual therapy vs exercise, Plot B (below) manual therapy vs drugs.

characteristics, in those seeking chiropractic care was estimated as ~308 people per 100,000 people per year regardless of treatment (Cashley et al., 2008). Cassidy et al. (2008) found that those under 45 years who had a vertebrobasilar artery stroke were three times more likely than controls to have visited a chiropractor or primary care physician beforehand. Both studies illustrate that those at risk of having a stroke or cervical artery dissection are those who are likely to visit either their general practitioner or manual therapist due to the nature of their symptoms, namely sudden onset severe unusual headache and/or neck pain and stiffness (Cashley et al., 2008; Cassidy et al., 2008).

3.2. Limitations and future research

Our review was comprehensive; we applied our previously developed definition of types of adverse events (Carnes et al., 2010) to allow comparison of data for the different treatment modalities. However, classifying manual therapies was difficult because they are often complex multiple interventions and to truly ascribe causality was impossible in this study.

Time frames for collecting data remain an issue. Some latency may be observed with arterial pathologies, between a few hours and months. Predisposing events may act as triggers, or be a cause. Where there is latency between the observed event and the stroke, the exact aetiology becomes even less clear (Rubinstein, 2008). The multi-factorial nature of cervical artery dissection (Rubinstein et al., 2005) means the exact cause of the pathology is even harder to determine. Many studies in this field are based on retrospective cases, cadavers and Doppler flow measures, all of which have methodological limitations, making research in this field complex.

Further analysis of the nature and type of adverse events also needs to be considered. The rigorous reporting of adverse events in manual therapy efficacy trials is essential to allow for future pooling of data for meta-analysis.

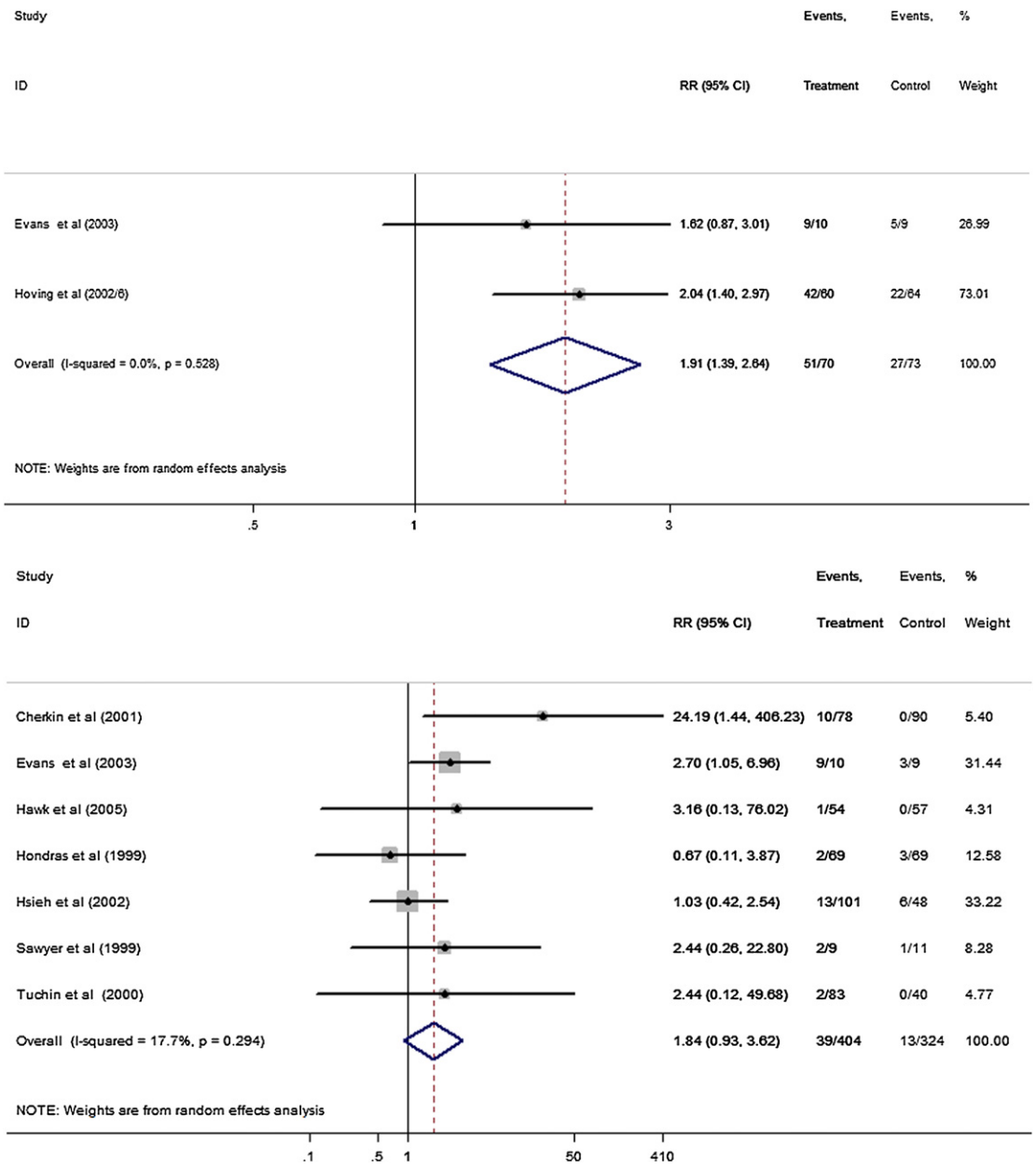

Fig. 3. Plot C manual therapy vs family practitioner/usual care, Plot D manual therapy vs sham/placebo/control.

4. Conclusion

Nearly half of patients after manual therapy experience adverse events that are short-lived and minor; most will occur within 24 h and resolve within 72 h. The risk of major adverse events is very low, lower than that from taking medication. We suggest that risk is inherent in all health interventions and should be weighed against patient-perceived benefit and alternative available treatments.

Competing interests

Dawn Carnes, Thomas Mars and Robert Froud are trained Osteopaths, there are no other competing interests

Contributors

Dawn Carnes was the Principle Investigator and managed the review and guarantees the scientific rigour and accuracy of the content of the paper. Tom Mars did the searches, selection of papers, data extraction and analysis with Dawn Carnes. Brenda Mullinger contributed advice and editing assistance, Martin Underwood provided expertise, advice and comments on each successive draft. Robert Froud gave statistical advice and produced the forest plots.

Funding

Funding was provided by the General Osteopathic Council (UK) via the National Council for Osteopathic Research (NCOR). All contributors had access to the original and raw data.

Ethics

No ethics approvals were required for this research.

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