research

Risk of colorectal cancer similar between half siblings and siblings p 437

SMT has similar effects as other options for chronic low back pain p 438

WHO targets for dietary intake of sodium and potassium questioned p 439

Around one in 20 hospital patients has troponin levels above the upper limit for normal p 440

ORIGINAL RESEARCH Nationwide cohort study

Familial colorectal cancer risk in half siblings and siblings

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Study question What is the risk of colorectal cancer in family members of patients with colorectal cancer?

Methods Using the world's largest population based family cancer dataset, this cohort study followed more than 16 million people in Sweden from 1958 to 2015. Of those with clear genealogy, 173 796 developed colorectal cancer. The lifetime (0-79 years) cumulative risk and relative risk of colorectal cancer among first and second degree relatives were calculated and compared. Family history was extracted from record linkage between genealogy data and Swedish Cancer Registry data, which are not subject to under-reporting by self reported family history.

Study answer and limitations The family history of colorectal cancer in half siblings was similarly associated with risk of colorectal cancer to that in siblings, and the increase in risk among people with only one affected second degree relative was negligible except for half siblings. An individual's risk of colorectal cancer was substantially increased when a second degree relative and a first degree relative (or even another second degree relative) were affected. Although information on some risk factors for colorectal cancer (for example, physical activity and dietary habits) was lacking, alternative adjustments were made for residential area, socioeconomic status, and hospital admission for obesity.

Relative risk of familial colorectal cancer by detailed relationship

Relationship*	No	Relative risk (95% CI)
1 half sibling+1 parent	32	3.6 (2.4 to 5.0)
1 half sibling+1 FDR	41	3.5 (2.5 to 4.8)
1 paternal half sibling+1 FDR	26	4.3 (2.8 to 6.2)
1 maternal half sibling+1 FDR	15	2.7 (1.5 to 4.5)
2 half siblings	6	3.5 (1.3 to 7.6)
1 half sibling+1 sibling	8	3.4 (1.4 to 6.6)
1 grandparent+1 FDR	82	3.0 (2.4 to 3.7)
1 sibling+1 parent	396	2.7 (2.4 to 3.0)
2 siblings	105	2.2 (1.8 to 2.7)
1 uncle/aunt+1 FDR	28	2.2 (1.4 to 3.1)
1 sibling	2089	1.7 (1.6 to 1.7)
1 brother	1165	1.7 (1.6 to 1.8)
1 sister	924	1.6 (1.5 to 1.7)
1 parent	5520	1.6 (1.5 to 1.6)
Father	2697	1.6 (1.5 to 1.6)
Mother	2823	1.6 (1.5 to 1.6)
1 half sibling	140	1.5 (1.3 to 1.8)
1 grandparent	460	1.2 (1.1 to 1.3)
1 uncle/aunt	189	1.2 (1.0 to 1.3)

FDR=first degree relative.
*All family histories are exclusive; for example, the risk reported for one affected half sibling does not include those with both an affected half sibling and any other affected first or second degree relative.

What this study adds A family history of colorectal cancer only in a half sibling has a much stronger association with increased risk of colorectal cancer than that in other second degree relatives, such as a grandparent or uncle/aunt. Having a family history of colorectal cancer in a half sibling might be handled similarly to having it in a sibling (or in general a first degree relative).

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Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain

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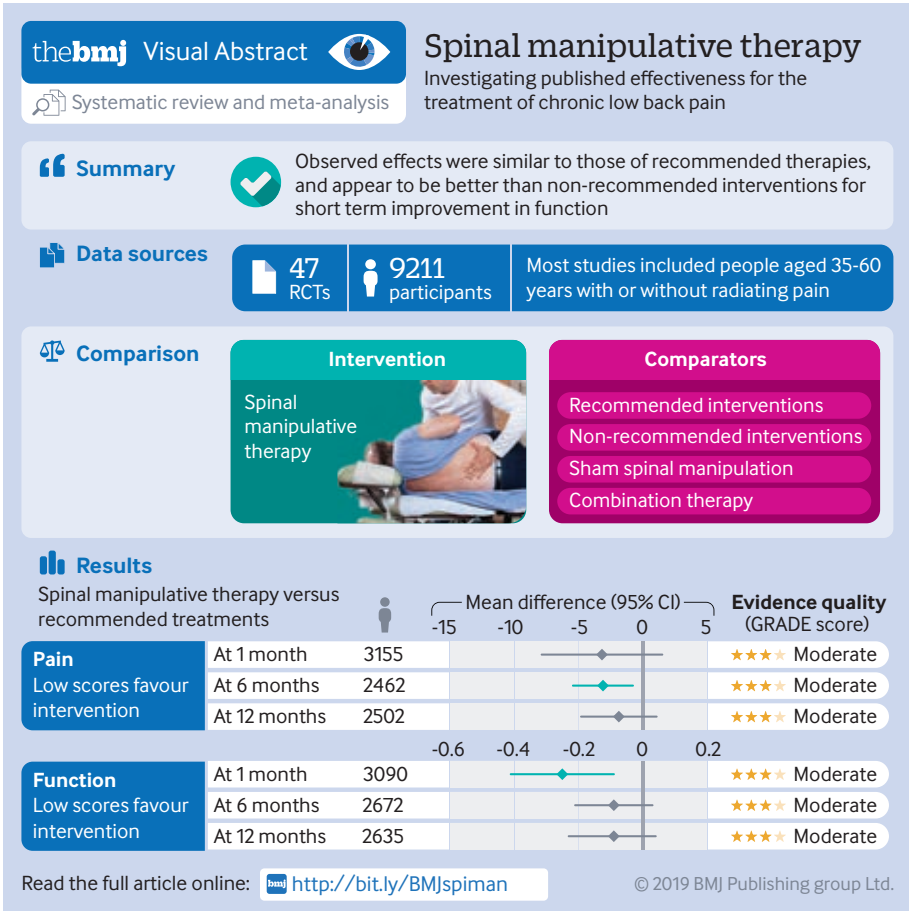
Study question Is spinal manipulative therapy (SMT) beneficial or associated with harm for the treatment of chronic low back pain?

Methods In this systematic review and meta-analysis, the authors conducted a comprehensive search of several databases and trial registries up to 4 May 2018, including reference lists of eligible trials and related reviews. Eligible studies were randomised controlled trials examining the effect of spinal manipulation or mobilisation in adults with chronic low back pain. The effect of SMT was compared with recommended therapies (eg, exercise, usual care provided by a general practitioner), non-recommended therapies (eg, light soft tissue massage, diathermy, ultrasonography), sham (placebo) SMT, and SMT as an adjuvant therapy. The main outcomes were pain relief and improvement in back specific functional status at the short (one month), intermediate (six months), and long term (12 months) follow-up.

Study answer and limitations 47 randomised controlled trials including 9211 participants were identified. Most trials compared SMT with recommended therapies; moderate quality evidence suggests that SMT has similar effects to other recommended therapies for short term pain relief (mean difference −3.17, 95% confidence interval −7.85 to 1.51), and a small, clinically better improvement in function (standardised mean difference −0.25, 95% confidence interval −0.41 to −0.09). Compared with non-recommended therapies, high quality evidence suggests that SMT results in a small, not clinically better effect for short term pain relief (mean difference −7.48, −11.50 to −3.47) and small to moderate clinically better improvement in function (SMD −0.41, −0.67 to −0.15). In general, these results were similar for the intermediate and long term outcomes, as well as for SMT as an adjuvant therapy. Evidence for sham SMT was of poor quality and, therefore, it should be considered of uncertain benefit. About half of the studies examined adverse and serious adverse events, but in most of these the methodology was unclear. Most of the observed adverse events were musculoskeletal related, transient in nature, and of mild to moderate severity. The most important limitation is the limited number of good quality studies.

What this study adds SMT produces similar effects as recommended therapies for chronic low back pain but seems to be better than non-recommended interventions for improvement in function in the short term. Patients should be fully informed about potential adverse events before treatment.

Funding, competing interests, and data sharing
No funding was received for this review. The protocol is registered with the Cochrane Library. SMR received personal grants from various chiropractic organisations for his position at the university. AdeZ received funding for a separate project, which examined the effects of SMT. Both work in clinical practice as chiropractors. Data on the characteristics of the included studies are available from the corresponding author.



Summary of treatment effects and GRADE summary of findings for spinal manipulative therapy (SMT) versus recommended therapies among trials included in systematic review

Outcomes by follow-up	Effect estimate* (95% CI)	No of studies	No of participants	I^2 (%)	Quality of evidence (reason for downgrading)
Pain:					
1 month	−3.17 (−7.85 to 1.51)	17	3155	92	Moderate (inconsistency)
6 months	−3.09 (−5.42 to −0.77)	11	2462	58	Moderate (inconsistency)
12 months	−1.86 (−4.79 to 1.07)	10	2502	69	Moderate (inconsistency)
Functional status:					
1 month	−0.25 (−0.41 to −0.09)	16	3090	76	Moderate (inconsistency)
6 months	−0.09 (−0.21 to 0.03)	12	2672	50	Moderate (inconsistency)
12 months	−0.09 (−0.23 to 0.04)	11	2635	62	Moderate (inconsistency)

GRADE=Grading of Recommendations Assessment, Development, and Evaluation.
*Data are mean difference for pain and standardised mean difference for functional status.

Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality

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Study question What is the joint association of sodium and potassium urinary excretion (as surrogate measures of intake) with cardiovascular events and mortality, in the context of current World Health Organization recommendations (‹2.0 g/day sodium, ›3.5 g/day potassium) for adults?

Methods The Prospective Urban Rural Epidemiological (PURE) Study is an international prospective cohort study involving 18 high, middle, and low income countries. The investigators obtained morning fasting urine samples from 103 570 people and estimated 24 hour sodium and potassium excretion. Using multivariable Cox regression, they examined the association of estimated urinary sodium and potassium excretion with all cause mortality and major cardiovascular events (median follow-up 8.2 years). A six category variable for joint sodium and potassium was generated: sodium excretion (low (‹3 g/day), moderate (3-5 g/day), and high (›5 g/day) sodium intakes) by potassium excretion (greater/equal, or less than median 2.1 g/day).

Study answer and limitations After a median follow-up of 8.2 years, 7884 (6.1%) participants had died or experienced a major cardiovascular event. Increasing urinary sodium excretion was positively associated with increasing potassium excretion (unadjusted r=0.34), and only 0.002% had a concomitant urinary excretion of ‹2.0 g/day of sodium and ›3.5 g/day of potassium. A J-shaped association was observed of sodium excretion and inverse association of potassium excretion with death and cardiovascular events. For joint sodium and potassium excretion categories, the lowest risk of death and cardiovascular events occurred in the group with moderate sodium excretion (3-5 g/day) and higher potassium excretion (21.9% of cohort). The estimate of sodium intake was based on a baseline measurement, derived from fasting morning urine samples rather than repeated 24 hour urine collections, which would be considered the reference standard for estimating usual sodium and potassium intake. Other limitations are those inherent in observational studies, such as residual confounding.

A J-shaped association was observed of sodium excretion and inverse association of potassium excretion with death and cardiovascular events

What this study adds These findings question the feasibility of combined WHO targets for sodium and potassium intake in the adult population and suggest that moderate (rather than low) sodium intake with higher potassium intake is associated with the lowest risk of cardiovascular events and mortality.

Funding, competing interests, and data sharing
See the full paper on bmj.com for multiple sources of funding. The current study is funded by the European Research Council and Heart and Stroke Foundation of Ontario. The authors have no financial relations with any organisations that might have influenced the submitted work. No additional data are available.

Association of joint urinary sodium and potassium excretion with mortality and cardiovascular events

Estimated potassium excretion (g/day)	Estimated sodium excretion (g/day)		
	‹3	3-5	›5
‹median, 2.1 g/day:			
Hazard ratio (95% CI)	1.23 (1.11 to 1.37)	1.10 (1.01 to 1.19)	1.21 (1.11 to 1.32)
Event proportion*	716/7582 (9.4%)	1924/24741 (7.8%)	1260/14259 (8.8%)
≥median, 2.1 g/day:			
Hazard ratio (95% CI)	1.19 (1.02 to 1.38)	1.00 (Reference)	1.10 (1.02 to 1.18)
Event proportion*	233/3420 (6.8%)	1454/22 688 (6.4%)	2297/30 510 (7.5%)

Adjusted for age (included as spline function), sex, education, current and former alcohol intake (units weekly), diabetes mellitus, body mass index, physical activity, history of cardiovascular events, use of cardiovascular drugs (blood pressure lowering, statins, or antidiabetics), history of tuberculosis, cancer, HIV, and current and former smoking.
*Event proportion for composite outcome of major cardiovascular events or mortality.

True 99th centile of high sensitivity cardiac troponin for hospital patients

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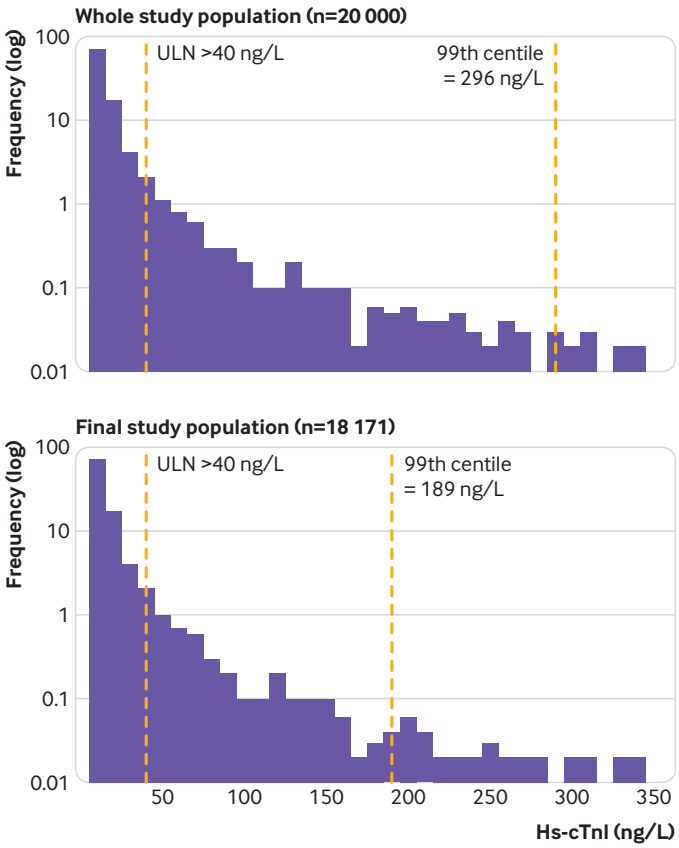
Study question What is the distribution, and specifically the true 99th centile, of high sensitivity cardiac troponin I (hs-cTnI) for an entire hospital population?

Methods This prospective study included 20 000 consecutive inpatients and outpatients undergoing blood tests for any clinical reason at University Hospital Southampton, a large teaching hospital. The study was conducted between 29 June 2017 and 24 August 2017. Hs-cTnI concentrations were nested for analysis in all study participants except when patients were discharged from hospital with a diagnosis of acute myocardial infarction or the supervising doctor had requested hs-cTnI for clinical reasons. The main outcome measure was the distribution of hs-cTnI concentrations of all study participants, and specifically the 99th centile.

Study answer and limitations The 99th centile of hs-cTnI for the whole study population was 296 ng/L compared with the manufacturer's recommended level of 40 ng/L (currently used clinically as the upper limit of normal; ULN). Hs-cTnI concentrations were greater than 40 ng/L in one in 20 (5.4%, n=1080) of the total population, in most of whom there was no clinical suspicion of acute myocardial infarction. After excluding participants diagnosed as having acute myocardial infarction (n=122) and those in whom hs-cTnI was requested for clinical reasons (n=1707), the 99th centile was 189 ng/L for the remainder (n=18 171). The 99th centile was 563 ng/L for inpatients (n=4759) and 65 ng/L for outpatients (n=9280). Patients from the emergency department (n=3706) had a 99th centile of 215 ng/L, with 6.1% (n=225) greater than the recommended ULN. A total of 39.0% (n=48) of all patients from the critical care units (n=123) and 14.2% (n=67) of all medical inpatients had an hs-cTnI concentration greater than the recommended ULN. This observational study had a large number of consecutive patients, so details about management and diagnoses could only be obtained from the best records available for each patient. In addition, because it was not part of the study objective, clinical outcomes were not examined.



Log distribution of high sensitivity cardiac troponin I (hs-cTnI) concentration in whole study population (n=20 000) and in final study population (n=18 171). ULN=upper limit of normal

What this study adds This study highlights the importance of interpreting the troponin result in hospital patients according to individual patients, their clinical presentation, and the guideline recommendations for correct diagnosis of type 1 and type 2 myocardial infarction. These results may help to avoid misdiagnosis and inappropriate treatment, and call into question the routine use of a manufacturer quoted 99th centile for an assay as a clinical ULN.

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Study registration ClinicalTrials.gov NCT03047785.