# Investigating the impact of randomized clinical trial reports

**Oh! what a tangled web we weave**
**When first we practise to deceive!**
**Sir Walter Scott, *Marmion***

**Fiona Stewart, University of Aberdeen**
**Alison Avenell*, University of Aberdeen**
**Andrew Grey, University of Auckland**
**Mark Bolland, University of Auckland**
**Greg Gamble, University of Auckland**

# Our presentation in three acts

I **Novel statistical investigation methods examining data integrity for 33 randomized trials in 18 journals from one research group**

II **Investigating the impact of retracted randomized clinical trial reports**

III **Reporting concerns about data integrity for 33 randomized trials in 18 journals from one research group: a narrative review**

# Conflict of interest statements

- None of the authors has a conflict to disclose
- All authors wish to improve the integrity of the research literature – more promptly

**Appendix e-1:**

**Table e-1A: 33 Randomized controlled trials carried out by the researchers.**

1. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1 alpha-hydroxyvitamin D3 and calcium supplementation. *Stroke* 1997;28:736-9.
2. Sato Y, Honda Y, Kuno H, Oizumi K. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K-deficient stroke patients. *Bone* 1998;23:291-6.
3. Sato Y, Kuno H, Kaji M, Saruwatari N, Oizumi K. Effect of ipriflavone on bone in elderly hemiplegic stroke patients with hypovitaminosis D. *Am J Phys Med Rehabil* 1999;78:457-63.
4. Sato Y, Manabe S, Kuno H, Oizumi K. Amelioration of osteopenia and hypovitaminosis D by 1alpha-hydroxyvitamin D3 in elderly patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999;66:64-8.
5. Sato Y, Asoh T, Kaji M, Oizumi K. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. *J Bone Miner Res* 2000;15:2487-94.
6. Sato Y, Honda Y, Kaji M, Asoh T, Hosokawa K, Kondo I, et al. Amelioration of osteoporosis by menatetrenone in elderly female Parkinson's disease patients with vitamin D deficiency. *Bone* 2002;31:114-8.
7. Sato Y, Kaji M, Kondo I, Yoshida H, Satoh K, Metoki N. Hyperhomocysteinemia in Japanese patients with convalescent stage ischemic stroke: effect of combined therapy with folic acid and mecobalamine. *J Neurol Sci* 2002;202:65-8.
8. Sato Y, Asoh T, Metoki N, Satoh K. Efficacy of methylprednisolone pulse therapy on neuroleptic malignant syndrome in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;74:574-6.
9. Sato Y, Metoki N, Iwamoto J, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. *Neurology* 2003;61:338-42.
10. Sato Y, Kanoko T, Yasuda H, Satoh K, Iwamoto J. Beneficial effect of etidronate therapy in immobilized hip fracture patients. *Am J Phys Med Rehabil* 2004;83:298-303.
11. Iwamoto J, Takeda T, Sato Y, Uzawa M. Comparison of effect of treatment with etidronate and alendronate on lumbar bone mineral density in elderly women with osteoporosis. *Yonsei Med J* 2005;46:750-8.
12. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Amelioration by mecobalamin of subclinical carpal tunnel syndrome involving unaffected limbs in stroke patients. *J Neurol Sci* 2005;231:13-8.
13. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip f patients with stroke: a randomized controlled trial. *JAMA* 2005;293:1082-8.
14. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis* 2005
15. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fra 65 years or older after stroke. *Arch Intern Med* 2005;165:1743-8.
16. Sato Y, Iwamoto J, Kanoko T, Satoh K. Amelioration of osteoporosis and hypovitaminosis D exposure in hospitalized, elderly women with Alzheimer's disease: a randomized controlled t *Miner Res* 2005;20:1327-33.
17. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture af elderly women. *Neurology* 2005;64:811-6.
18. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and e plus calcium supplementation in elderly women with Alzheimer disease: a randomized contr *Arch Intern Med* 2005;165:1737-42.
19. Sato Y, Kanoko T, Satoh K, Iwamoto J. Menatetrenone and vitamin D2 with calcium supplen nonvertebral fracture in elderly women with Alzheimer's disease. *Bone* 2005;36:61-8.
20. Iwamoto J, Takeda T, Sato Y, Uzawa M. Effect of whole-body vibration exercise on lumbar density, bone turnover, and chronic back pain in post-menopausal osteoporotic women treate alendronate. *Aging Clin Exp Res* 2005;17:157-63.
21. Sato Y, Honda Y, Iwamoto J. Etidronate for fracture prevention in amyotrophic lateral sclero randomized controlled trial. *Bone* 2006;39:1080-6.
22. Sato Y, Iwamoto J, Kanoko T, Satoh K. Alendronate and vitamin D2 for prevention of hip fr Parkinson's disease: a randomized controlled trial. *Mov Disord* 2006;21:924-9.
23. Sato Y, Honda Y, Iwamoto J. Risedronate and ergocalciferol prevent hip fracture in elderly Parkinson disease. *Neurology* 2007;68:911-5.
24. Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H. Comparison of effects of alendronate and raloxifene on lumbar bone mineral density, bone turnover, and lipid metabolism in elderly women with osteoporosis. *Yonsei Med J* 2008;49:119-28.
25. Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H. Comparison of the effects of alendronate and alfacalcidol on hip bone mineral density and bone turnover in Japanese men having osteoporosis or osteopenia with clinical risk factors for fractures. *Yonsei Med J* 2009;50:474-81.
26. Iwamoto J, Suzuki H, Tanaka K, Kumakubo T, Hirabayashi H, Miyazaki Y, et al. Preventative effect of exercise against falls in the elderly: a randomized controlled trial. *Osteoporos Int* 2009;20:1233-40.
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28. Iwamoto J, Makita K, Sato Y, Takeda T, Matsumoto H. Alendronate is more effective than elcatonin in improving pain and quality of life in postmenopausal women with osteoporosis. *Osteoporos Int* 2011;22:2735-42.
29. Sato Y, Honda Y, Umeno K, Hayashida N, Iwamoto J, Takeda T, et al. The prevention of hip fracture with menatetrenone and risedronate plus calcium supplementation in elderly patients with Alzheimer disease: a randomized controlled trial. *Kurume Med J* 2011;57:117-24.
30. Sato Y, Iwamoto J, Honda Y. Once-weekly risedronate for prevention of hip fracture in women with Parkinson's disease: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2011;82:1390-3.
31. Sato Y, Iwamoto J, Honda Y. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:22-6.
32. Sato Y, Iwamoto J, Honda Y. An open-label trial comparing alendronate and alphacalcidol in reducing falls and hip fractures in disabled stroke patients. *J Stroke Cerebrovasc Dis* 2011;20:41-6.
33. Iwamoto J, Sato Y, Takeda T, Matsumoto H. Whole body vibration exercise improves body balance and walking velocity in postmenopausal osteoporotic women treated with alendronate: Galileo and Alendronate Intervention Trail (GAIT). *J Musculoskelet Neuronal Interact* 2012;12:136-43.



**33 RCTs**

**1997-2012**

**N= 6253**

**26 Authors**

**12 Institutions**

# Timeline

- **Our investigations started at the end of 2012**
- **May 2017 – only 11/33 trial reports retracted**
- **Misconceptions persist, e.g. 2015 JBMR**

modest effects of calcium and vitamin D which were provided to the control groups in each of these studies. Pharmacologic treatment is also more effective in reducing hip fracture risk in elderly patients with a history of Alzheimer's disease or with Parkinson's disease than is vitamin D alone.[20,21] In contrast to


20. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med. 2005 Aug 8–22;165(15):1737–42.
21. Sato Y, Iwamoto J, Honda Y. Once-weekly risedronate for prevention of hip fracture in women with Parkinson's disease: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2011 Dec;82(12):1390–3.

# Aims

- **To investigate the extent of citation of trial reports from this group in secondary publications, including:**
  - **clinical trials**
  - **systematic reviews**
  - **guidelines**
- **To examine the impact of the trial reports in these publications**
- **To discuss the issues raised by our investigation and how best to correct the evidence base**

# Methods (1)

- **We examined the impact of potentially the most influential trial reports of**
  - **Potent oral bisphosphonates, e.g. alendronate**
  - **Vitamin K**
  - **Vitamin D analogues**
  - **Vitamin B12 and /or folate**
- **Had to report hip fracture as an outcome**

- **Reports also had to be in higher impact journals**
  - **(ISI Web of Knowledge impact factor ≥ 4)**

**12/33 RCT reports to investigate**

**6/12 retracted so far……**

# Methods (2)

- **Excluded from our analysis reviews and meta-analyses by the two main authors under investigation, where they cited their own work**
  - **24 reviews**
    - **Sato = 5**
    - **Iwamoto = 19**
  - **Meta-analyses**
    - **Iwamoto = 7 (3 retracted)**

# Methods (3)

- **August 2016**
  - **Citation searching in Scopus for total numbers of citations**
  - **Citation searching in Google Scholar, PubMED, ISI Web of Science for**
    - **clinical trials**
    - **systematic reviews**
    - **guidelines**

- **Assessing impact on publications**
  - **Findings likely to change**
  - **Unclear if findings would change**
  - **Findings unlikely to change**

# Methods (4)

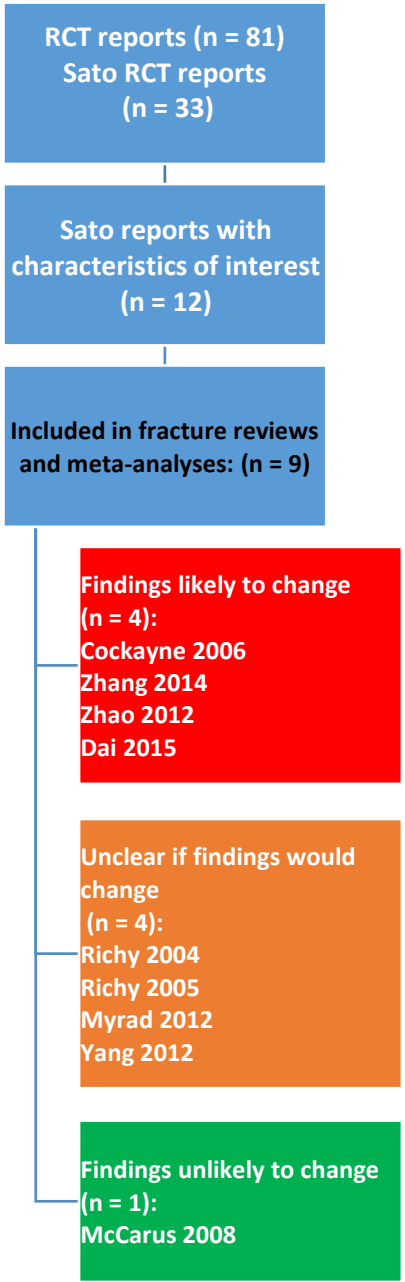
- **Rerun meta-analyses (rarely possible)**
- **One researcher assessed, checked by a second**
  - **Discussed differences**
  - **Reference to a third researcher if still uncertain about impact**
- **With a view to alerting affected publications**

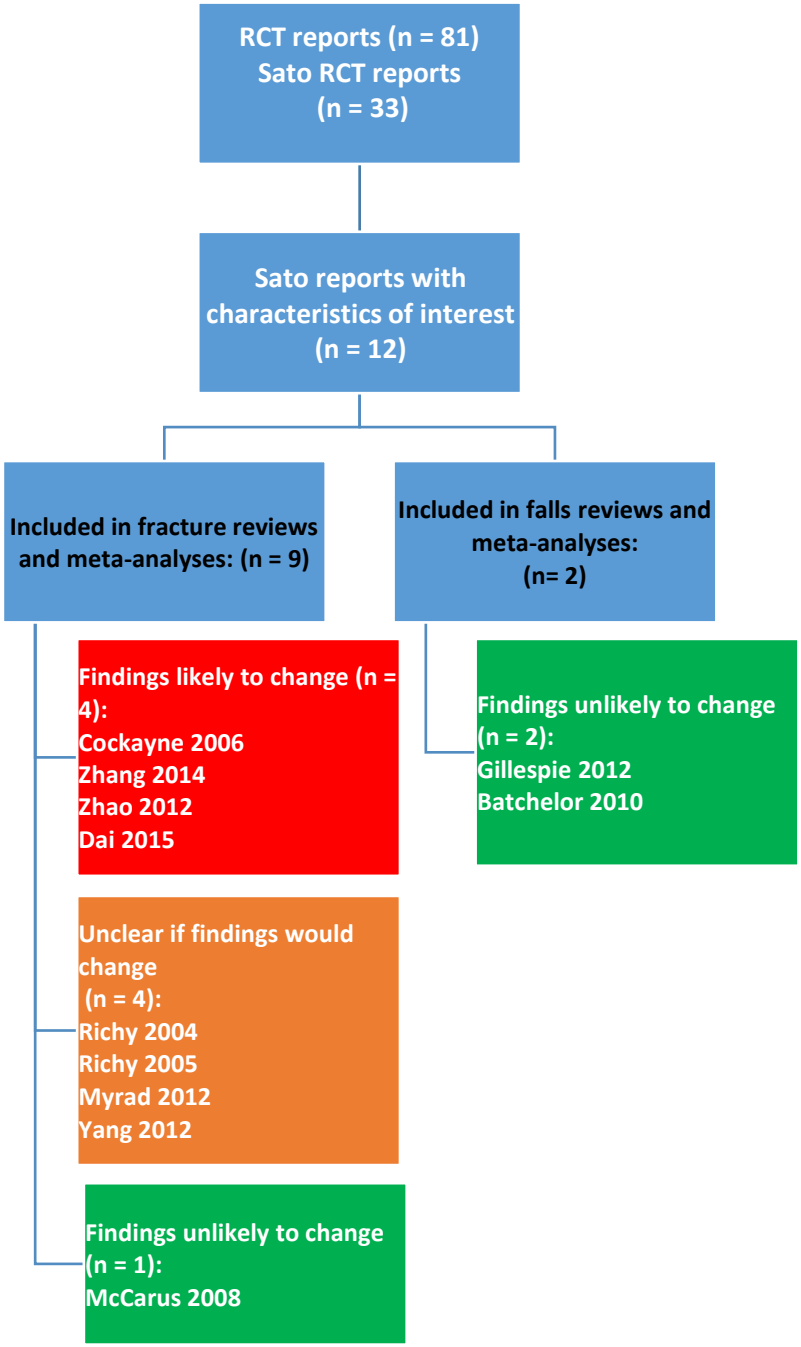
# Results

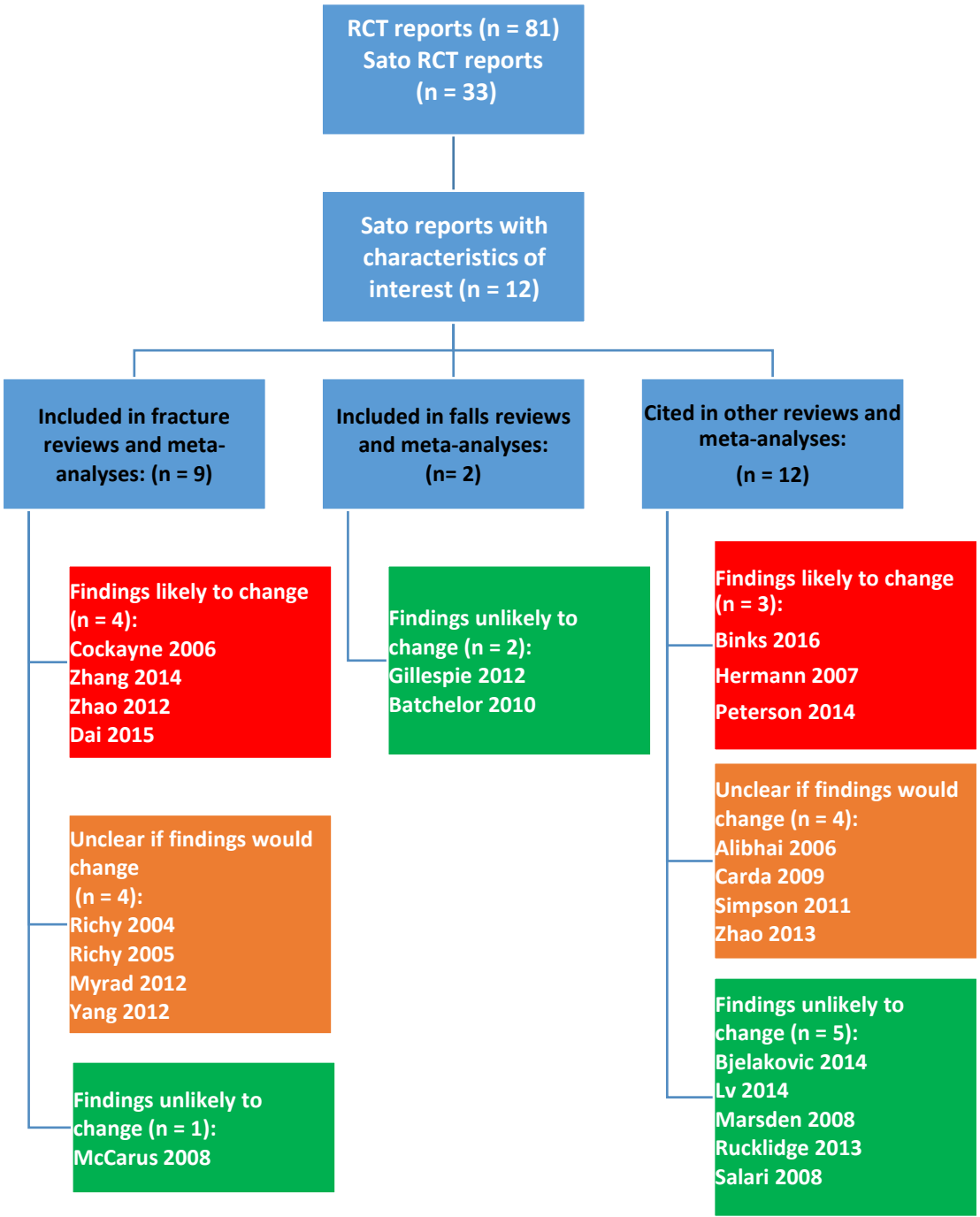
- **12/33 RCT reports**
  - **2956 participants**
  - **703 citations, excluding self-citations**
  - **Median number of citations 40 (range 6 to 208)**
    - **All reported a significant reduction in hip fractures**
    - **6/6 reported a reduction in non-vertebral fractures**
    - **11/11 reported significant improvements in BMD**
    - **9/9 reported no significant effect on falls**

- **Highest cited trial report**
  - **JAMA 2005;293:1082-8**

# Permeation of 12 RCT reports in secondary publications




RCT reports (n = 81)
Sato RCT reports
(n = 33)
Sato reports with characteristics of interest
(n = 12)
Included in fracture reviews and meta-analyses: (n = 9)
Included in falls reviews and meta-analyses:
(n= 2)
Findings likely to change (n = 4):
Cockayne 2006
Zhang 2014
Zhao 2012
Dai 2015
Findings unlikely to change (n = 2):
Gillespie 2012
Batchelor 2010
Unclear if findings would change
(n = 4):
Richy 2004
Richy 2005
Myrad 2012
Yang 2012
Findings unlikely to change (n = 1):
McCarus 2008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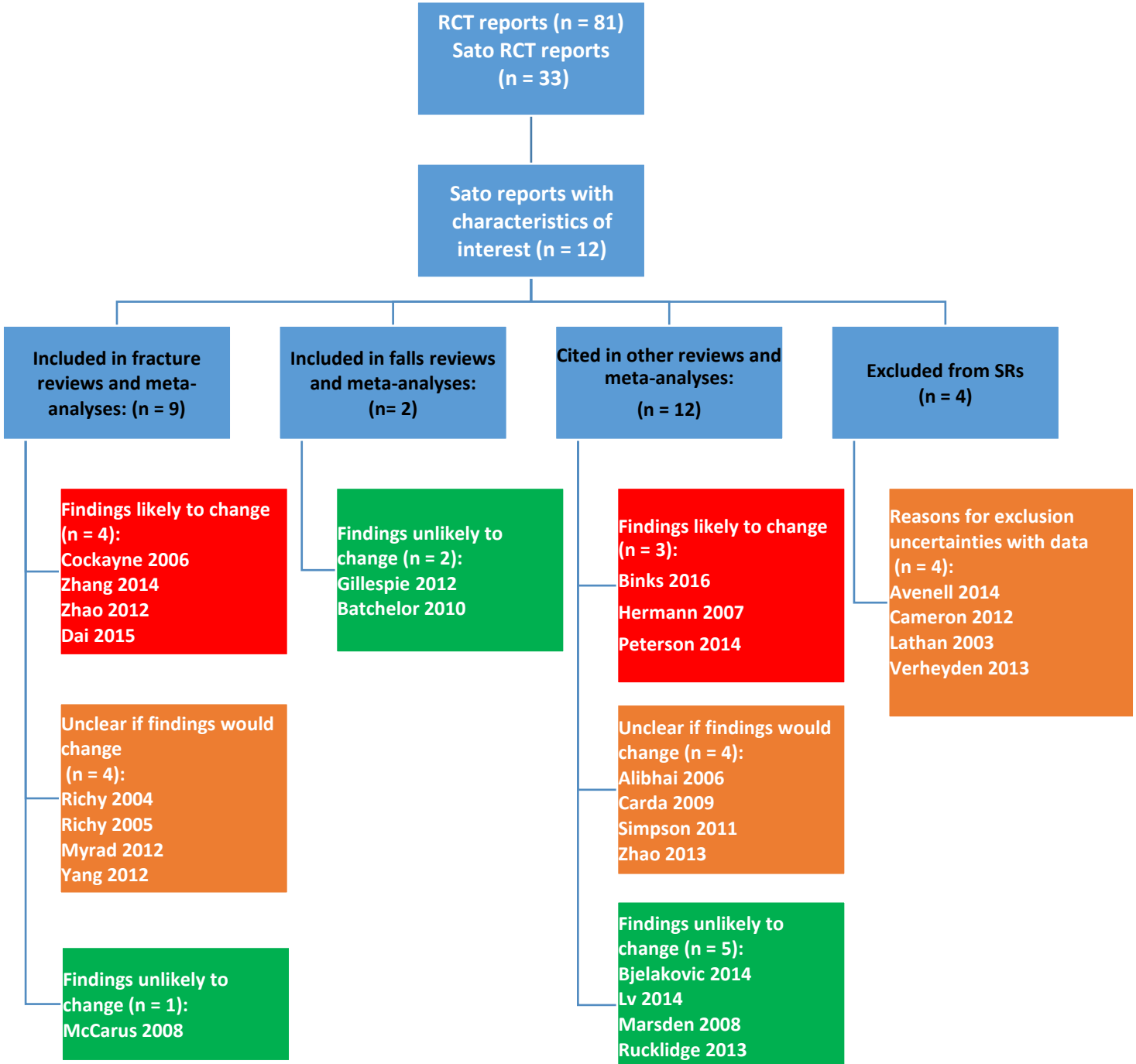
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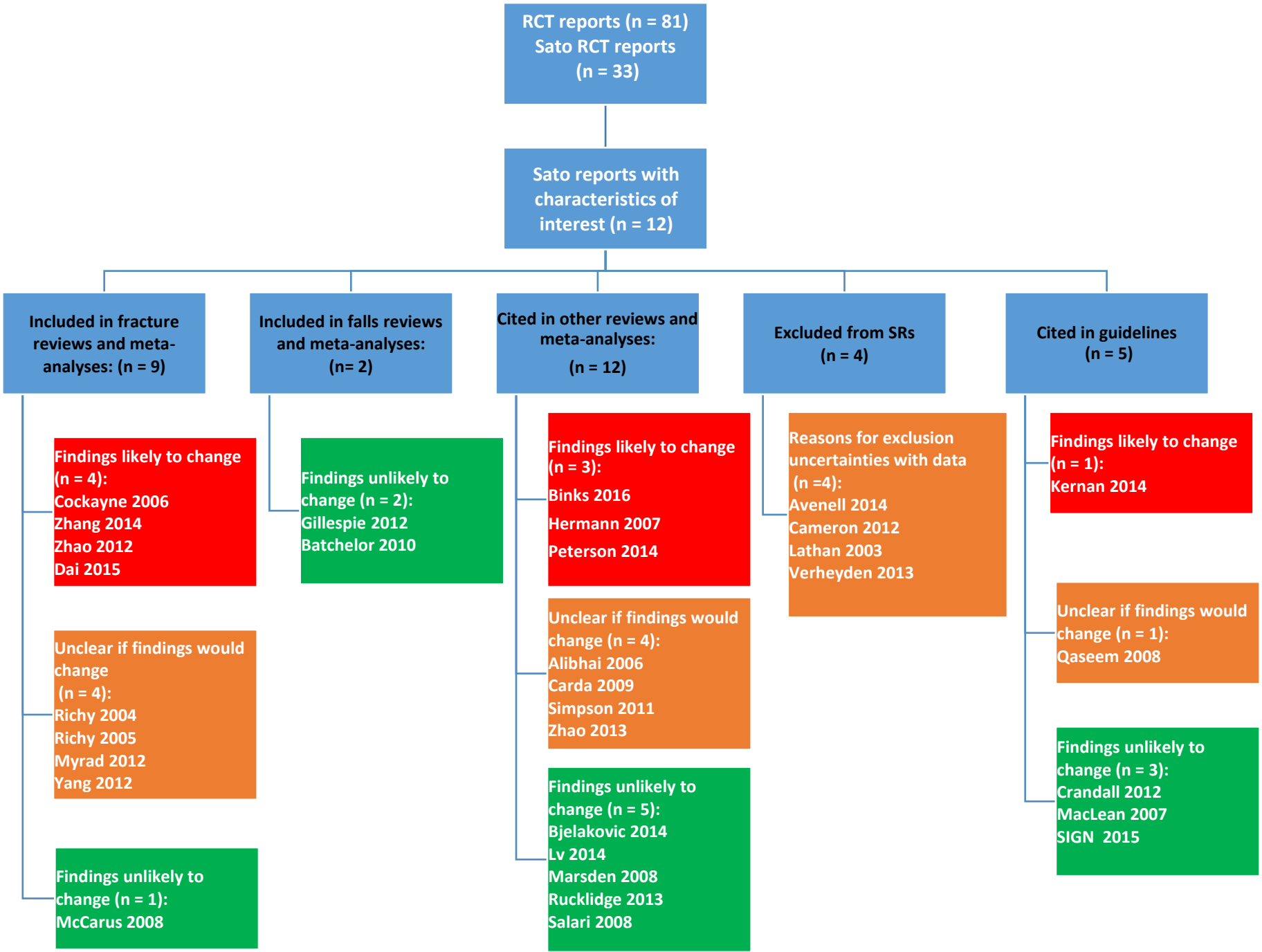
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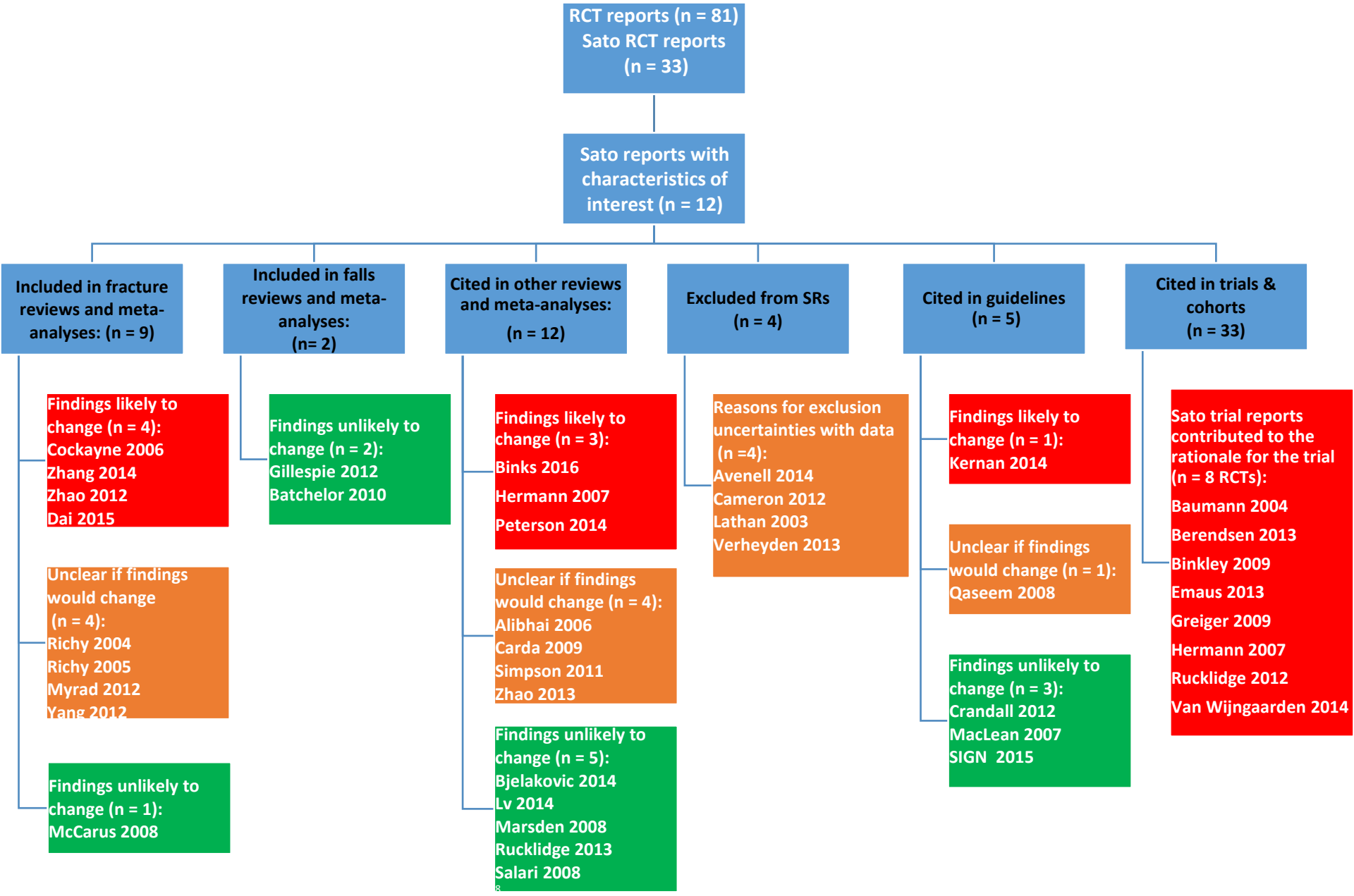
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Findings likely to change (n = 1):
Kernan 2014
Unclear if findings would change (n = 1):
Qaseem 2008
Findings unlikely to change (n = 3):
Crandall 2012
MacLean 2007
SIGN 2015
Cited in trials & cohorts (n = 33)
Sato trial reports contributed to the rationale for the trial (n = 8 RCTs):
Baumann 2004
Berendsen 2013
Binkley 2009
Emaus 2013
Greiger 2009
Hermann 2007
Rucklidge 2012
Van Wijngaarden 2014

# RCTs citing Sato trial reports in rationale

- 5107 participants in 8 RCTs citing Sato trial reports in rationale
- Size ranged from n = 40 to n = 2919
- B-PROOF trial (van Wijngaarden 2014):
  - B-vitamins for the prevention of fractures (Am J Clin Nutr 2014;100:1578-6)
  - 2919 participants
  - Recruitment 2008 – 2011
  - Follow-up for 2 years

# B-PROOF

prevalent in 30–50% of persons aged >65 y (15, 16). Treatment with vitamin B-12 and folic acid, which both play a central role in homocysteine metabolism (17), is effective in normalizing homocysteine concentrations (18, 19). Three randomized controlled trials investigated the effect of B-vitamin supplementation on fracture risk (20–22). Among stroke survivors (mean age: 71 y), a large protective effect of 2-y supplementation of 1.5 mg vitamin B-12 and 5 mg folic acid was observed on hip fracture risk in the trial by Sato et al (21). However, in the Heart Outcomes Prevention Evaluation-2 (HOPE-2)[6] trial, no effect of 5-y supplementation of 1 mg vitamin B-12, 2.5 mg folic acid, and 50 mg vitamin B-6 was observed on fracture incidence in persons with high cardiovascular disease risk (mean age: 69 y) (22). In the VITAmins TO Prevent Stroke (VITATOPS) study, there was also no effect of treatment with 2 mg folic acid, 25 mg vitamin B-6, and 500 $\mu$g vitamin B-12 during a mean of 2.8 y on osteoporotic fracture incidence observed in patients with cerebrovascular disease (mean age: 63 y) (20). Given the conflicting results and low generalizability to the general older population, further investigation is needed.

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**€1,700,000?**

# JAMA June 2016

EDITORIAL

## Notice of Retraction: Sato Y, et al. Effect of Folate and Mecobalamin on Hip Fractures in Patients With Stroke: A Randomized Controlled Trial. *JAMA*. 2005;293(9):1082-1088.

Howard Bauchner, MD; Phil B. Fontanarosa, MD, MBA

**In reaffirming** our previous Expression of Concern,[1] the article "Effect of Folate and Mecobalamin on Hip Fractures in Patients With Stroke: A Randomized Controlled Trial" by Sato et al[2] has been retracted due to acknowledgment of scientific misconduct resulting in concerns regarding data integrity and inappropriate assignment of authorship.

ARTICLE INFORMATION

**Author Affiliations:** Dr Bauchner is Editor in Chief and Dr Fontanarosa is Executive Deputy Editor, *JAMA*.

**Corresponding Author:** Howard Bauchner, MD (howard.bauchner@jamanetwork.org).

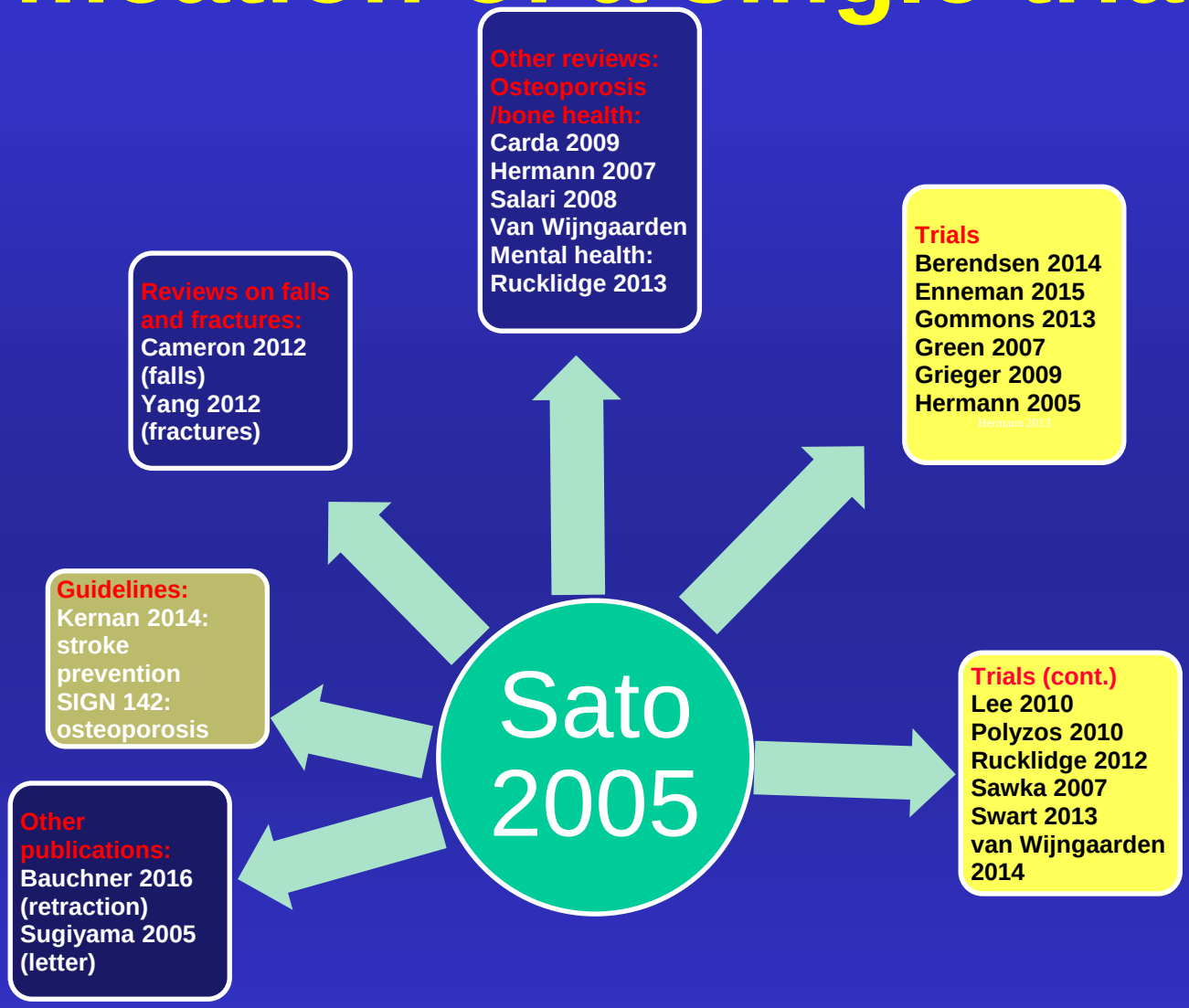
**Published Online:** June 3, 2016. doi:10.1001/jama.2016.7190.

REFERENCES

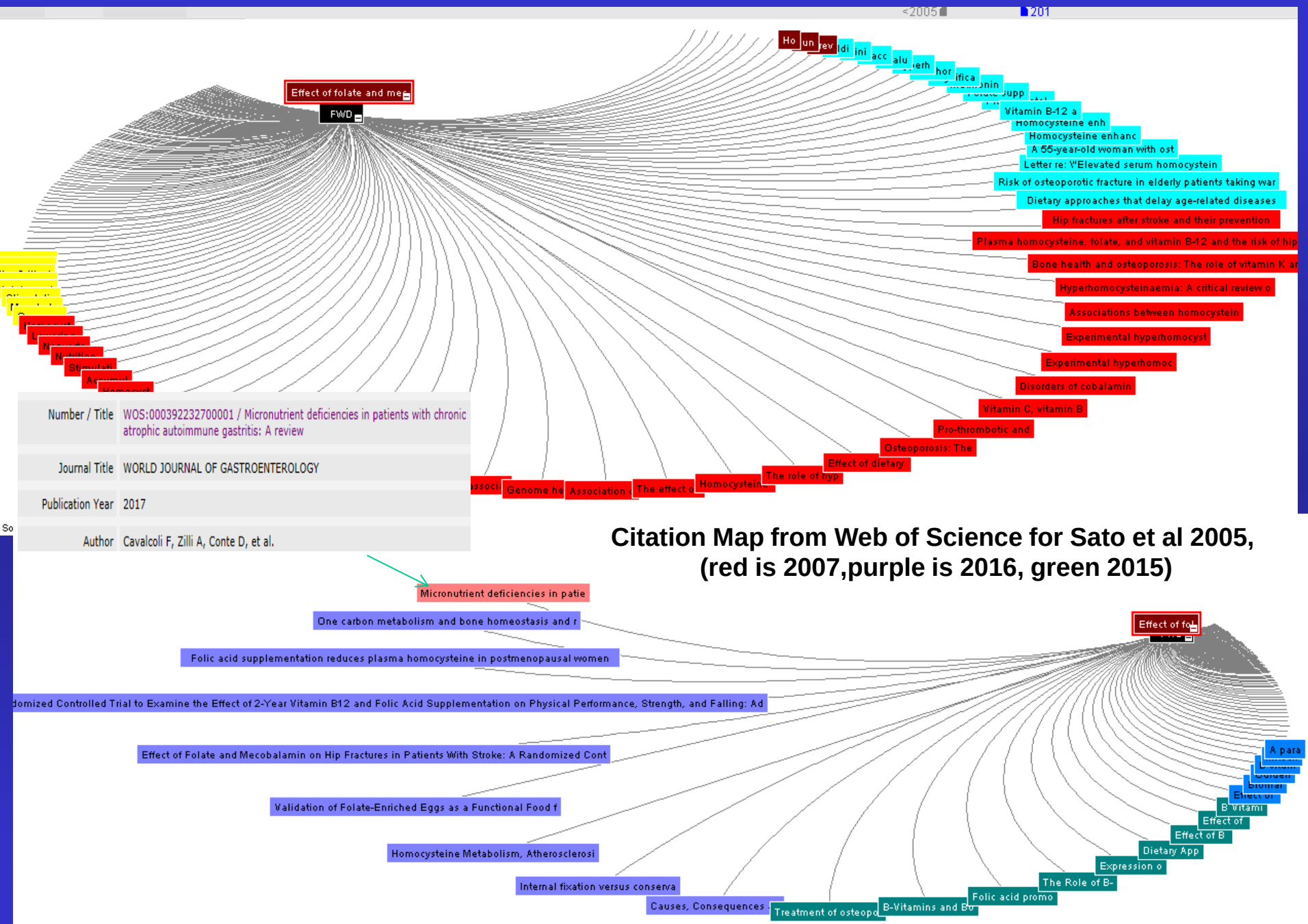
1. Bauchner H, Fontanarosa PB. Expression of concern: Sato et al. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293(9):1082-1088. *JAMA*. 2015;313(19):1914.

2. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293(9):1082-1088.

# Permeation of a single trial report



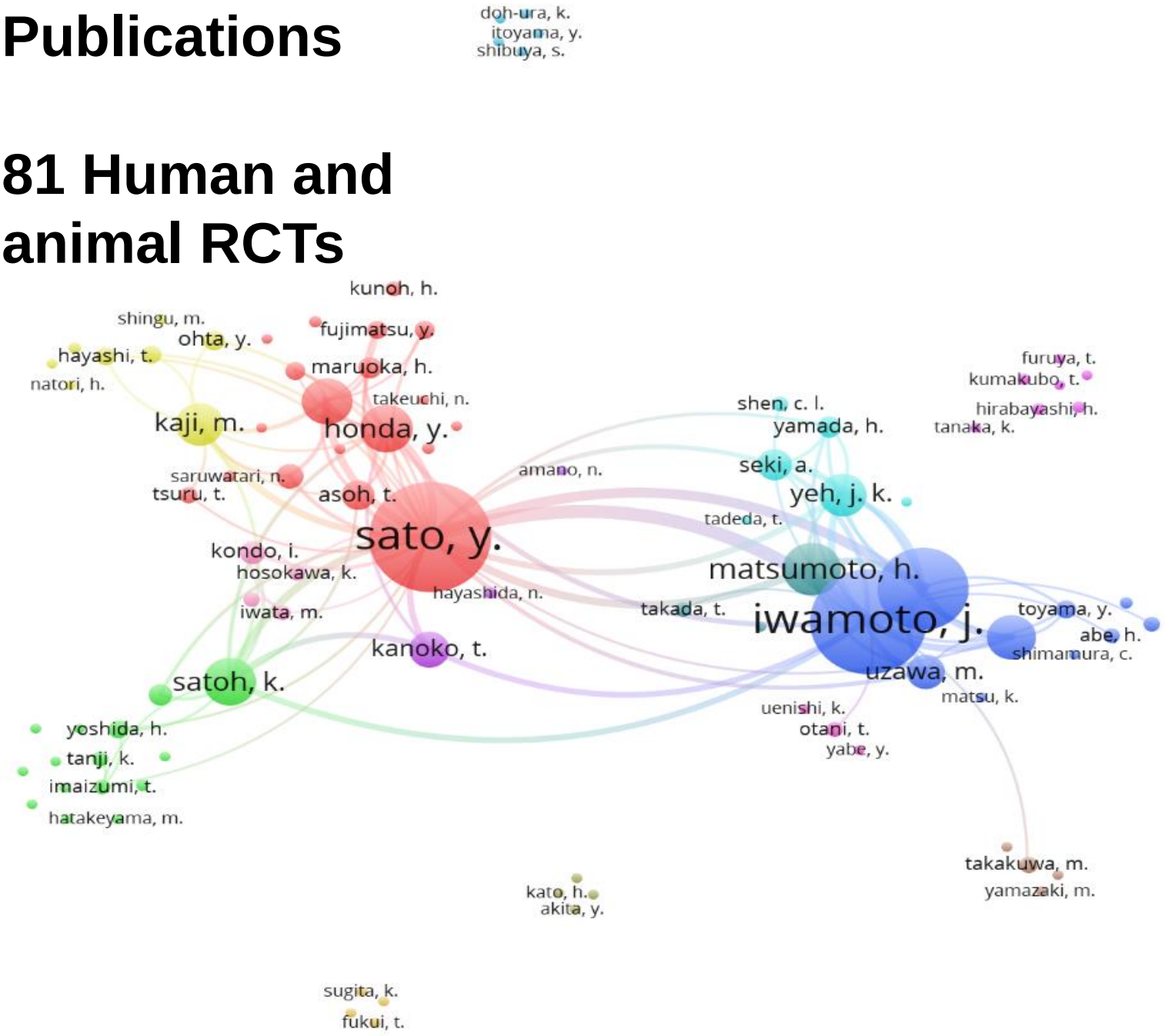

Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. JAMA. 2005;293(9):1082-8

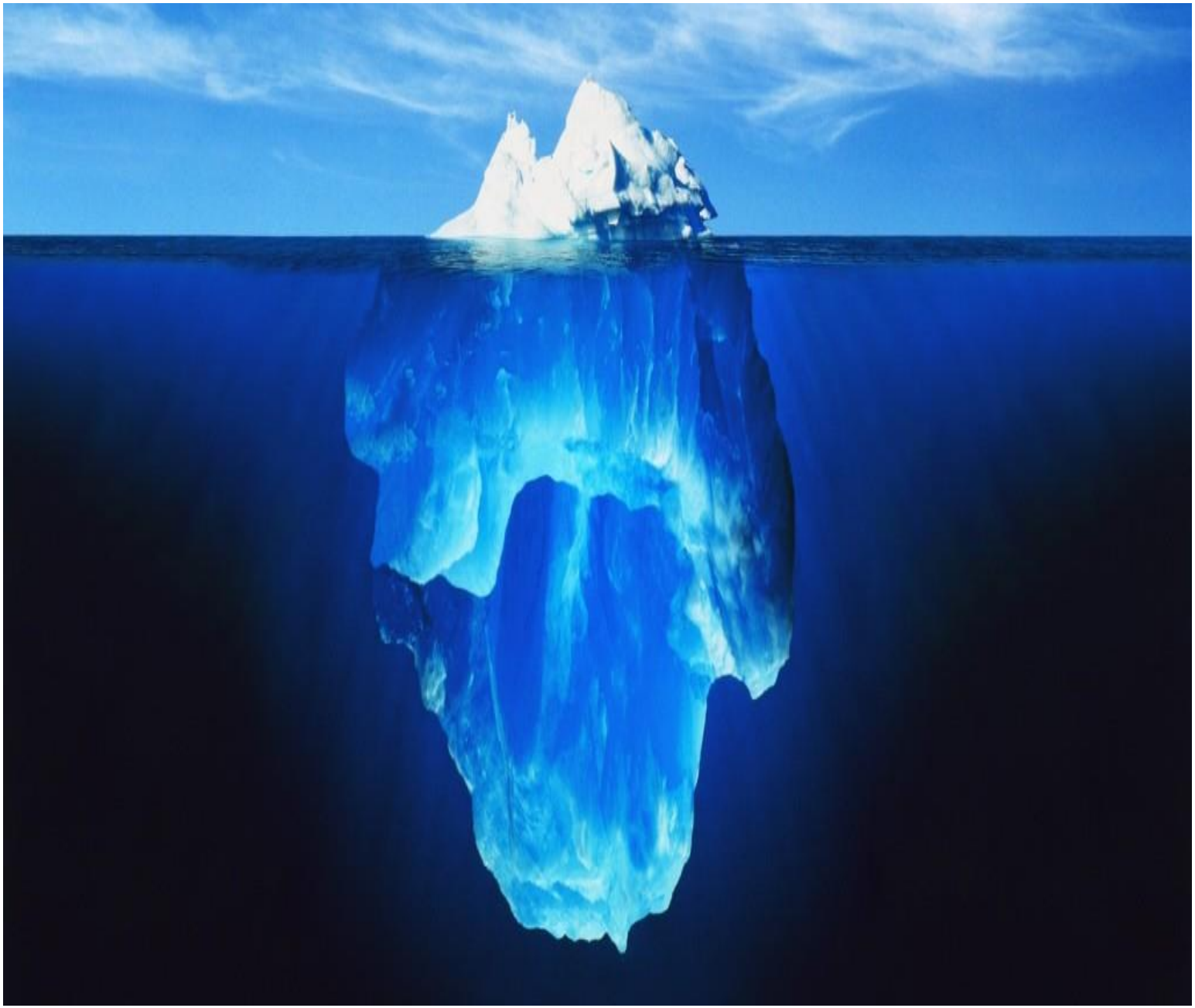



**Citation Map from Web of Science for Sato et al 2005, (red is 2007,purple is 2016, green 2015)**

**>220 Publications**

**81 Human and animal RCTs**





# For discussion

1. **Authors and editors of secondary affected publications**
   - **At what stage should they be alerted – EoC, retraction?**
   - **How should this happen – via editors, learned societies, institutions, database alerts?**

2. **What about wider influences outside affected publications?**
   - **Tertiary affected publications…?**
   - **Influences beyond publications, e.g. media?**

3. **Who is there to advise on this?**

4. **Who should coordinate this?**

5. **Who should fund all of this?**

6. **What consequences for the researchers investigated?**

**Acknowledgements**

**Bill Gillespie (Hull York Medical School, UK)**

**Lesley Gillespie (University of Otago, New Zealand)**

**David Torgerson (University of York, UK)**

**Mari Imamura, Research Fellow and native Japanese speaker (University of Aberdeen, UK)**

**Doug Altman and anonymous referees for their comments**

**Numerous colleagues who listened and advised**