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Contrasting adverse effects associated with low and high nicotine concentration electronic cigarettes (EC): a systematic review meta-analysis

Mr. Aathavan Shanmuga Anandan^{1,2}, Dr. Daniel Stjepanovic¹, Dr. Gary Chan¹

¹National Centre for Youth Substance Use Research, ²Faculty of Medicine, The University of Queensland

Introduction

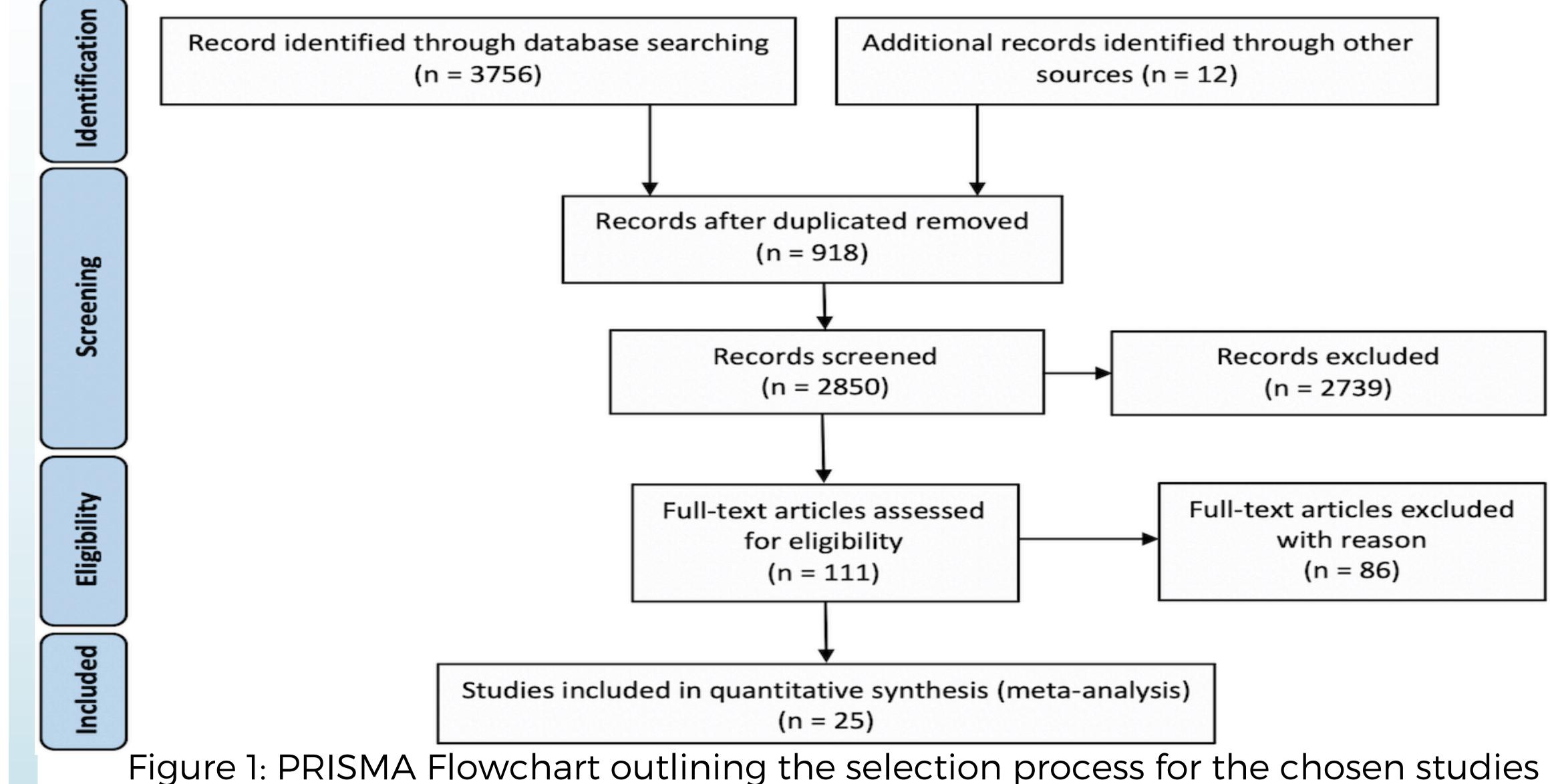
The use of alternative forms of nicotine delivery as an aid for tobacco cessation is the current mainstream approach to harm reduction and smoking cessation.

The role of electronic cigarettes (ECs) as a tool for quitting tobacco is contentious with safety and adverse effects (AEs) commonly cited as criticisms against its use.

This systematic review compares the adverse effects associated with a low nicotine concentration (LNC) (<6mg/mL) versus high nicotine concentration (HNC) (>6mg/mL) in ECs. The use of the 6mg/mL this is threshold was chosen minimum the considered standard concentration nicotine conventional tobacco cigarette.

Methods

- Studies reporting quantitative data on common AEs were included in final data extraction
- Database search for EC adverse effects executed on PubMed, Web of Science & PsycINFO
- Database search resulted in 2850 unique entries (post-duplicate removal) with 25 papers included in final analysis
- Studies were subsequently differentiated into low nicotine concentration (LNC) (<6mg/mL) and high nicotine concentration (HNC) (>6mg/mL) sub-groups
- Ultimately, of the 25 articles, 9 reported LNC AEs and 16 reported HNC AEs



included in the final synthesis

Discussion

Overall, results indicate that HNC ECs were associated with a greater incidence of:

Vertigo (OR = 1.86) Cough (OR = 1.65)

Nausea (OR = 2.86) Oral Irritation (OR = 2.09)

Contrarily, LNC ECs induced a greater incidence of:

Headache (OR = 0.52)

HNC ECs were associated with a greater reported side effect incidence of vertigo, nausea, cough and oral irritation. These symptoms are explainable by the elevated nicotine concentration, replicating common nicotine exposure symptoms.

LNC ECs noted a greater incidence of headache. The apparent increase in incidence of headache in LNC ECs was attributed to the effects of nicotine withdrawal in smokers attempting cessation therapy. Headache/migraines are an established AE of nicotine withdrawal, and the lack of supplemental nicotine in LNC ECs may have resulted in the experience of withdrawal.

The current systematic review noted two key limitations. Firstly, the review did not adjust for covariates and thus reported unadjusted odds ratios (OR). Furthermore, the review contained EC users which were a mix between never tobacco smokers, ex-smokers and current tobacco smokers. The variation in experience of smoke inhalation may have led to variation in results and reduced generalisability to the general population.

This research provides an effective benchmark to understand the AEs associated LNC and HNC in electronic cigarettes. To further compound on this research, clinical trials investigating the optimal concentration of nicotine to minimise adverse effects could be conducted. Additionally, trials noting the nicotine concentration associated with the greatest adherence to tobacco cessation therapy would provide high practical relevance.

Results

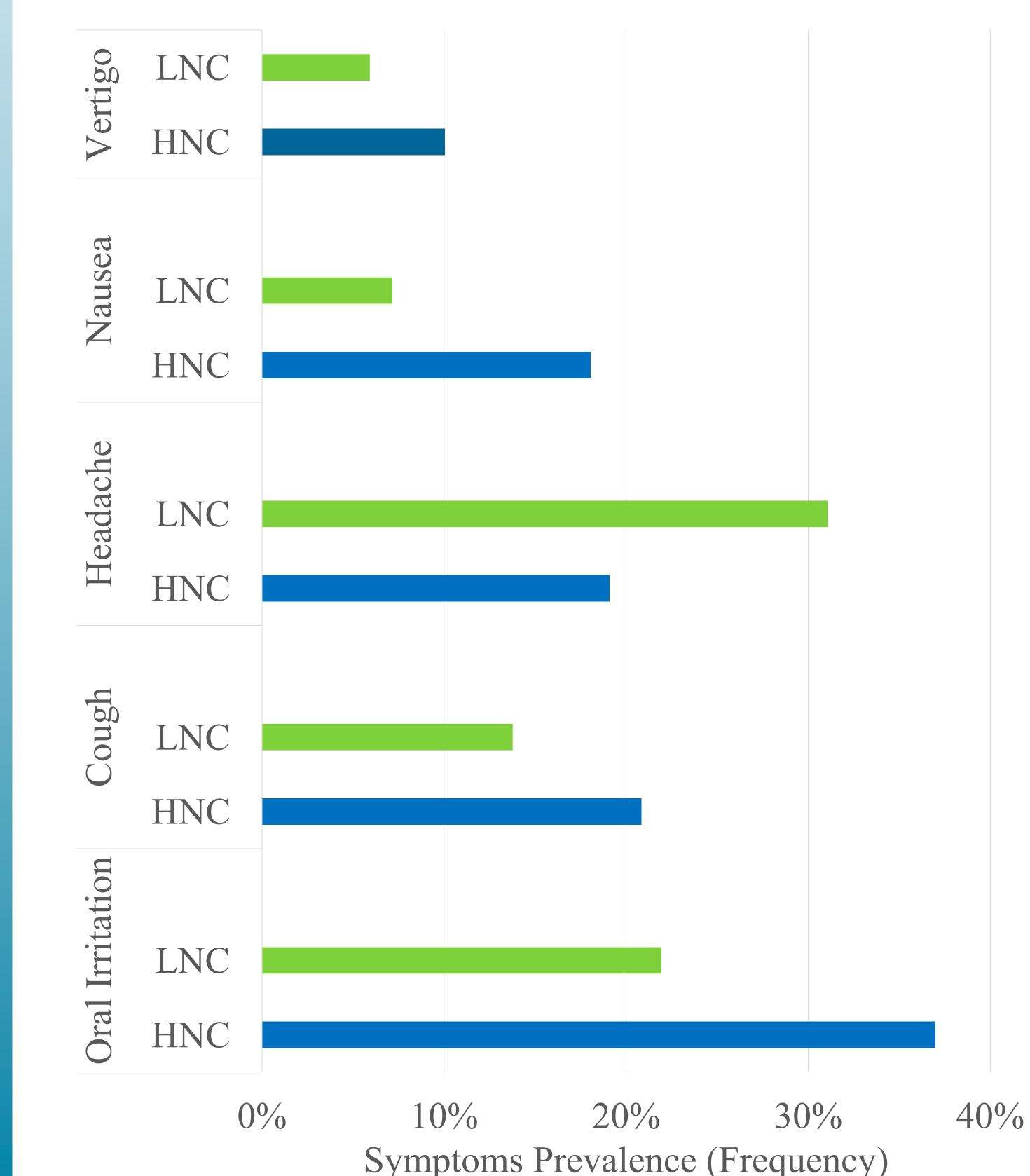


Figure 2: Comparison of the joint adverse effects (AEs) between low nicotine concentration (LNC) electronic cigarettes (EC) and high nicotine concentration (HNC) electronic cigarette (EC).

HNC ECs were more associated with oral irritation (OR = 2.09), cough (OR = 1.65), vertigo (OR = 1.86), nausea (OR = 2.86).

Contrarily LNC ECs were suggested to be more prone in causing headache (OR = 0.52)

Comparing the effectiveness of nicotine electronic cigarettes (ECs) and nicotine replacements therapies (NRTs): a systematic network meta-analysis

Mr. Aathavan Shanmuga Anandan^{1,2}, Dr. Daniel Stjepanovic¹, Dr. Gary Chan¹, Ms. Carmen Lim¹, Ms. Tianze Sun¹, Dr. Jason Connor^{1,3}, Dr. Coral Gartner⁴, Prof. Wayne Hall¹, Dr. Janni Leung¹

National Centre for Youth Substance Use Research, ²Faculty of Medicine, The University of Queensland, ³Discipline of Psychiatry, The University of Queensland, ⁴School of Public Health, The University of Queensland

Introduction

The ineffectiveness of traditional nicotine replacement therapies (NRTs) in achieving complete cessation highlights the need for novel therapeutic approaches.

Electronic cigarettes (EC) are potential smoking cessation aids that provide both nicotine and behavioural substitution for combustible cigarette smoking. Current literature has highlighted the effectiveness of both ECs and NRTs in achieving a degree of cessation.

This review aims to compare the effectiveness of nicotine e-cigarettes for smoking cessation with licensed nicotine replacement therapies (NRTs) and control conditions by using network meta-analysis (NMA).

Methods

- Randomised controlled trials (RCTs) involving healthy ex-smokers allocated to either nicotinic ECs or NRT/placebo were included
- PubMed, Web of Science & PsycINFO searched for articles
- Database search for NRTs resulted in 1014 unique entries (post-duplicate removal) with 9 trials satisfying the inclusion criteria
- Database search for ECs resulted in 4717 unique entries (post-duplicate removal) with 8 trials ultimately included in final analysis
- A NMA was conducted for the 9 NRT trials and the 8 EC trials

Results

| Comparison | Number of Studies | Direct Evidence | Random effects model | RR | 95%-CI |
|--|----------------------|--------------------|----------------------|--------|--|
| control:Nicotine Direct estimate Indirect estimate Network estimate | 5 | 0.36 | | 1.81 | [1.49; 4.90] [1.16; 2.83] [1.46; 2.99] |
| control:NRT Direct estimate Indirect estimate Network estimate | 9 | 0.92 | | - 1.99 | [1.07; 1.73] [0.87; 4.57] [1.11; 1.77] |
| NRT:Nicotine EC Direct estimate Indirect estimate Network estimate | 4 | 0.81 | 0.5 1 2 | 2.09 | [0.97; 1.95] [1.01; 4.31] [1.09; 2.04] |

Figure 1: Forest plot of the decomposition of estimates computed from the direct and indirect comparison. All the direct and indirect estimates were largely consistent, and Z-tests indicated that these effects were not significantly different in the three comparisons (all p-values > 0.30). An overall test indicated no evidence of inconsistency between direct and indirect estimates, Q(3) = 1.13, p = .769.

Figure 2: Comparison-adjusted funnel plots. The plot is largely symmetrical, and Egger's test also indicated that there was no evidence of asymmetry (p = .706), suggesting an absence of publication bias.

Discussion

Overall, the study found two primary conclusions:

- 1. Participants randomised to receive nicotine e-cigarettes were 49% more likely to remain abstinent from smoking than those who received NRTs (pooled RR = 1.49, 97.5% CI = [1.04, 2.14]).
- 2. Those randomised to receive nicotine e-cigarettes were 109% more likely to remain abstinent from smoking than those in control conditions where no nicotine was supplied (pooled Risk Ratio (RR) = 2.08, 97.5% CI = [1.39, 3.15]).

Although three key limitations were noted with the findings of this review:

- 1. One of the seven e-cigarette trials was a pilot study and four had a sample size of 100 or fewer participants per treatment condition, reducing generalisability of findings to the general population
- 2. There is a moderate level of heterogeneity ($I^2 = 42\%$). in the trials in this study. This is likely due to the considerable variation in e-cigarettes and NRT products used in different trials, and the possibility that effectiveness may vary between these products.
- 3. The majority of the studies had relatively short follow-up periods of 6 months or less, and therefore we had limited data on long term abstinence.

This review establishes the utility of nicotine ECs as a cessation tool, contrasting against existing front-line cessation aids that are more frequently utilised. Public policy may seek to encourage heavy smokers to utilise e-cigarettes as a means to reduce or quit smoking tobacco products. Future research is necessary to understand the long-term implications of EC use due to the limited data in this area.

Contrasting adverse effects of electronic cigarettes (ECs) with traditional nicotine replacement therapies (NRTs): a systematic review meta-analysis

Mr. Aathavan Shanmuga Anandan^{1,2}, Dr. Daniel Stjepanovic¹, Dr. Gary Chan¹

¹National Centre for Youth Substance Use Research, ²Faculty of Medicine, The University of Queensland

Introduction

Tobacco is a leading cause of preventable death in Australia, with high relapse for established nicotine replacement therapies (NRTs).

Adverse effects (AEs) associated with cessation therapies are commonly cited for discontinuation.

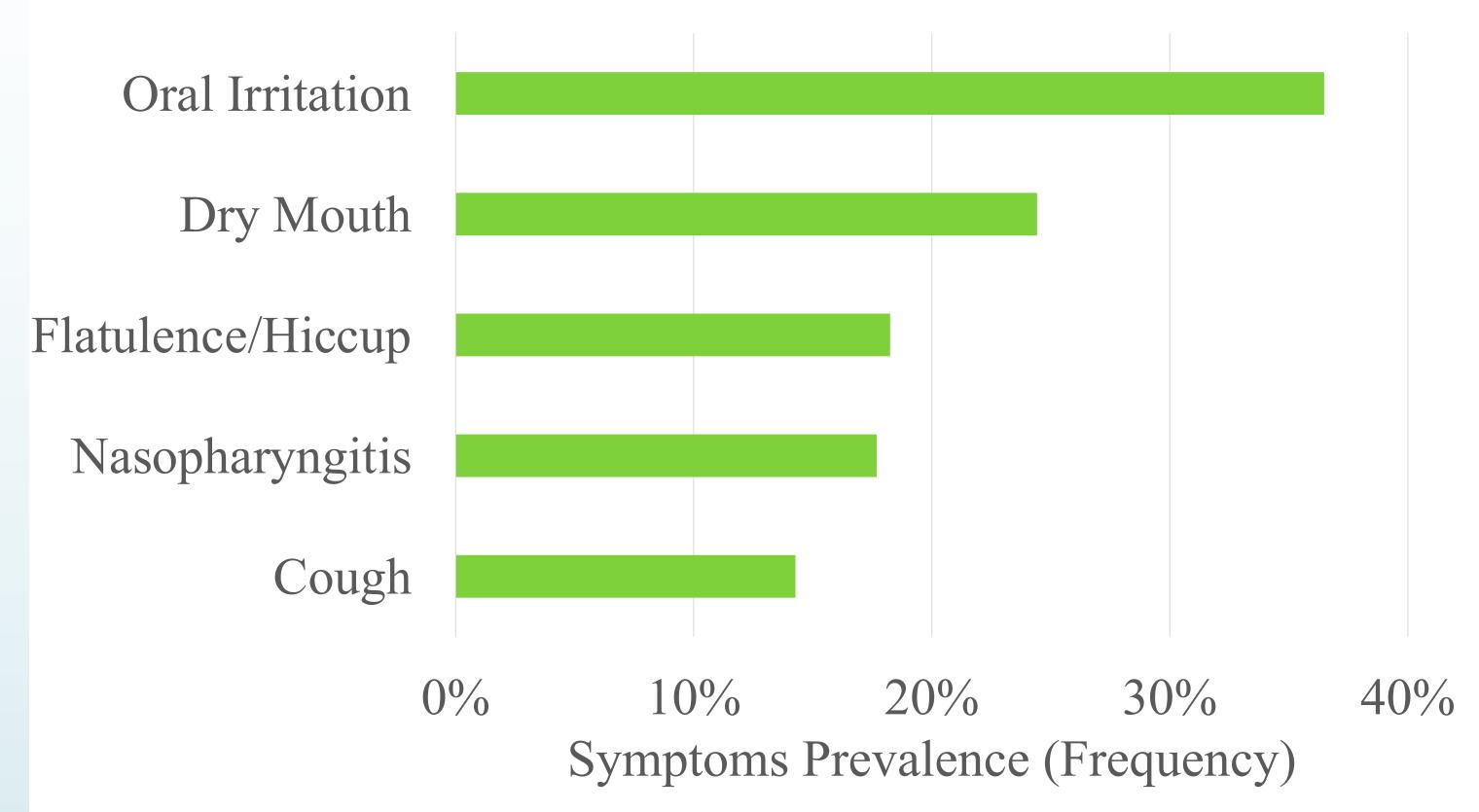
development of electronic cigarettes (EC), their role as a smoking cessation aid has been theorised.

This systematic review compares the side effect profiles of traditional NRTs (i.e. patches, gums, lozenges, sprays) with EC nicotine delivery.

Methods

- Studies reporting quantitative data on common AEs were included in final data extraction
- Database search for EC adverse effects executed on PubMed. Web of Science & PsycINFO
- search resulted Database unique entries (post-duplicate removal) with 39 papers (28,424 participants) being used in final synthesis
- Comparison of AEs made to review by Mills et al. (2010): 120 papers (177,390 participants) used in final synthesis

Results



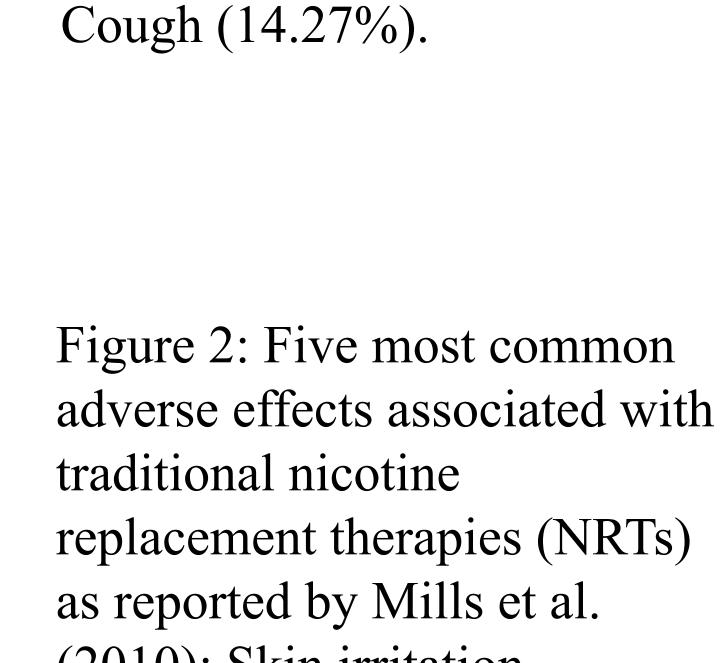


Figure 1: Five most common

adverse effects associated with

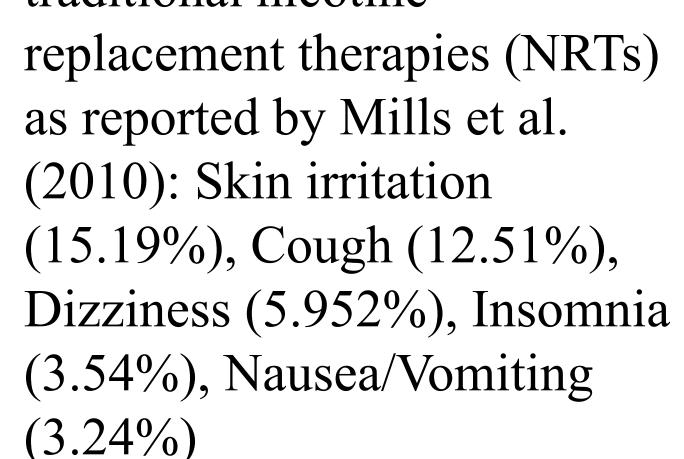
electronic cigarette (EC): Oral

Mouth (24.42%), Flatulence/

Nasopharyngitis (17.69%),

Irritation (36.49%), Dry

Hiccup (18.24%),



20%

40%

Skin irritation Cough Vertigo Overall, results indicate that ECs were associated with a greater incidence of: Headache (OR = 5.01) Insomnia Insomnia (OR = 2.30) Nausea/Vomitting

0%

Contrarily, NRTs induced a greater incidence of:

Vertigo (OR = 0.97)

Cough (OR = 1.16)

Discussion

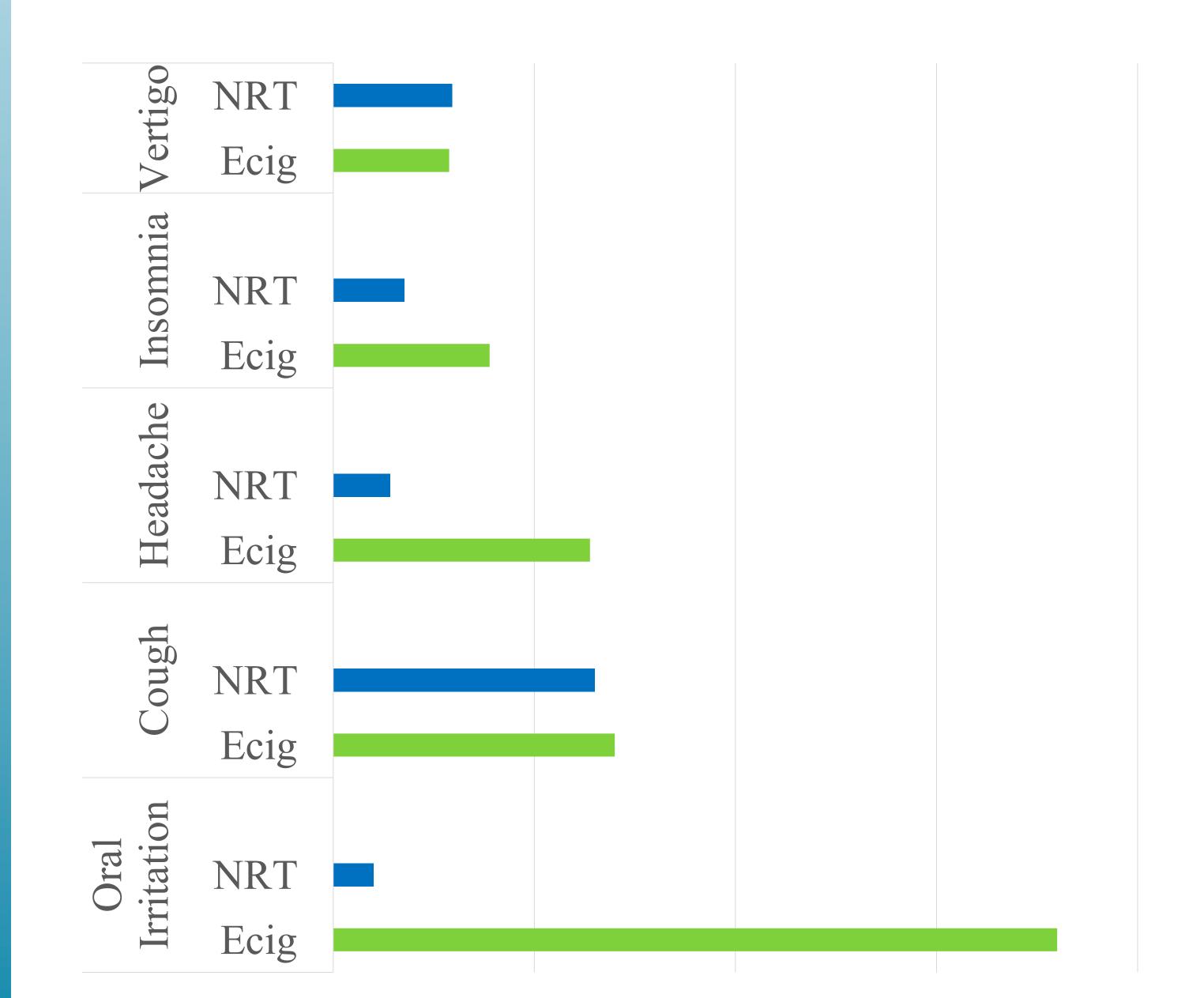
Oral Irritation (OR = 32.15)

Understanding the negative health implications of commonly prescribed cessation therapies is essential in determining whether a sphere exists for the role of ECs. The most common AEs associated with EC use were consistent with those linked with tobacco use such as oral irritation, dry mouth, nasopharyngitis and cough. This suggests that tolerability of these AEs would be greater in tobacco users attempting ECs as a cessation tool. Contrarily, the most common NRT AEs are not considered common side effects of tobacco consumption such as skin irritation, insomnia and nausea/vomiting. The unfamiliarity of NRT's AEs in smokers attempting cessation may result in reduced abstinence rates.

Three key limitations of the study were noted:

- Studies within the review, primarily Farsalinos et al. (2014) contributed to 19,353 of the 28,424 participants in the EC adverse effect pool leading to biased overrepresentation.
- 2. This review did not adjust for covariates such as duration of treatment, nicotine concentration used and participant demographics and only reported unadjusted ORs.
- 3. This study whilst observing the frequency of AEs, did not address the severity and level of impediment for each symptom, thus not wholly addressing factors affecting adherence to cessation therapy.

This review effectively quantifies frequency of common clinical presentations associated with mainstream cessation aids. Future work could seek to understand the experiential nature of traditional NRTs and ECs by quantifying not only the adverse events but also the favourable experiences of users, providing an avenue to enhance adherence.



Symptoms Prevalence (Frequency)

Symptoms Prevalence (Frequency)

Figure 3: Comparison of the joint adverse effects between electronic cigarettes (EC) and traditional nicotine replacement therapies (NRTs). ECs are more associated with oral irritation (OR = 32.15), cough (OR =1.16), headache (OR = 5.01) and insomnia (OR = 2.30).

Contrarily, NRTs were suggested to be more prone in inducing dizziness (OR = 0.97).

Brain Injuries in Children with Congenital Heart Disease: A Systematic Review and Meta-Analysis

Gautam Dagur^{1,2}, MD-PhD Candidate; Theresa I. Chin¹, PhD Candidate; Jake A. Kleinmahon^{2,3}, MD; Michelle Z. Gurvitz^{4,5}, MD; & Samudragupta Bora¹, PhD

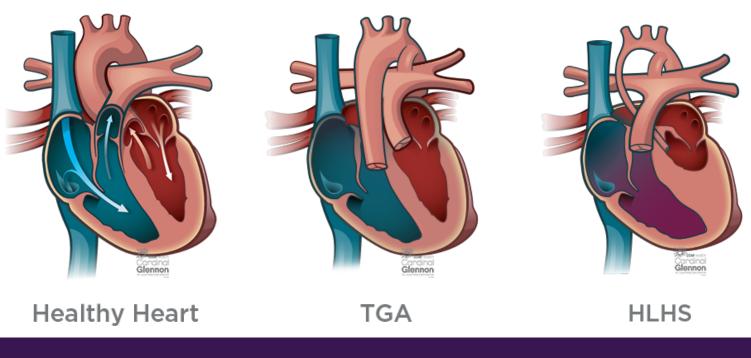
1. Mothers, Babies and Women's Health, Mater Research Institute, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia 2. Ochsner Clinical School, Faculty of Medicine, The University of Queensland, New Orleans, LA, USA

3. Pediatric Cardiology, Ochsner Hospital for Children, New Orleans, LA, USA
4. Pediatrics, Harvard Medical School, Boston, MA, USA

5. Cardiology, Boston Children's Hospital, Boston, MA, USA

BACKGROUND

- ➤ Congenital heart disease (CHD) is the most prevalent congenital malformation and the leading cause of infant mortality.
- ➤ Over the past few decades there has been an increase in prevalence and a decrease in mortality of CHD, due to improvements in surgical advancements.
- > Children with CHD are at risk of brain injuries.
- ➤ However, the extent and nature of these injuries remain unclear due to small sample sizes, typically single timepoint focus, and varying neuroimaging modalities.



OBJECTIVE

➤ To determine the prevalence and nature of brain injuries in children with CHD as detected on magnetic resonance imaging (MRI) during prenatal, postnatal-preoperative, and postoperative periods.

METHODS

- > PRIMSA guidelines were strictly followed:
 - Two independent reviewers screened databases (CINAHL, EMBASE, PsycINFO, PubMed, and SCOPUS) and relevant reference list.
- Studies included if:
- Publications in English until December 2019;
- Nonsyndromic children <21 years with CHD and reported brain injury on structural MRI;
- During prenatal, postnatal-preoperative, and postoperative.

RESULTS

- > 88 independent studies meeting criteria (Figure 1).
- Pooled sample size included 371, 1865, and 1973 children with CHD for prenatal, postnatal-preoperative, and postoperative analysis, respectively.
- ➤ Pooled prevalence of brain injuries 22% for prenatal, 35% for postnatal-preoperative, and 50% for postoperative period (Figure 2-4).
- Predominant brain injuries were ventriculomegaly (10%) for prenatal and white matter injury for both preoperative (24%) and postoperative (30%) (Figure 5-7).

FIGURES

Figure 1. PRISMA Study Selection Flowchart.

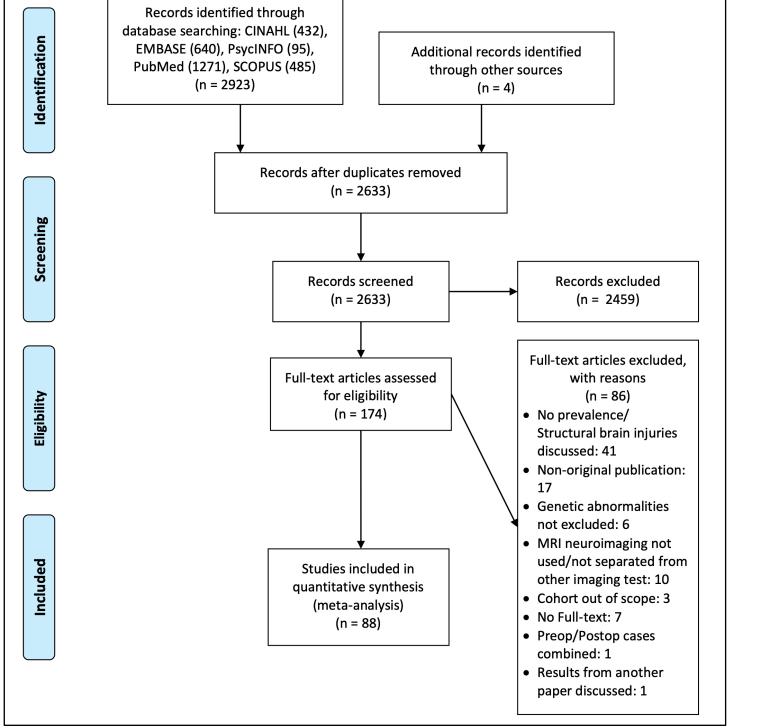


Figure 2. Prenatal Prevalence of Brain Injuries in Fetuses with Congenital Heart Disease.

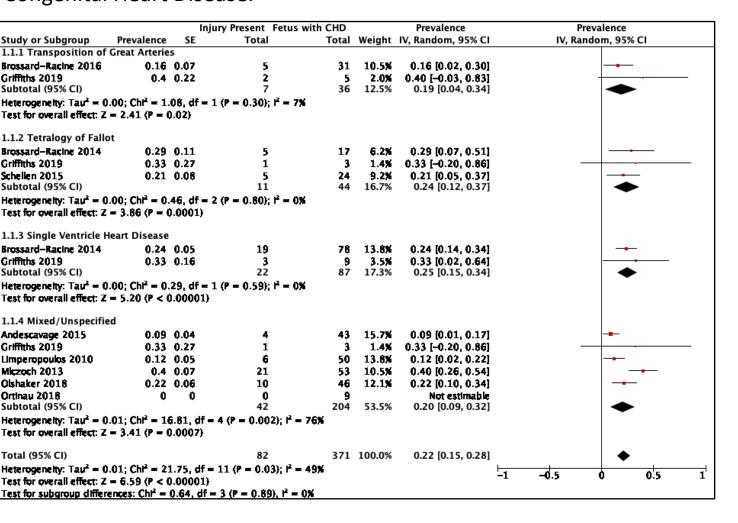


Figure 3. Postnatal-Preoperative Prevalence of Brain Injuries in Children with Congenital Heart Disease.

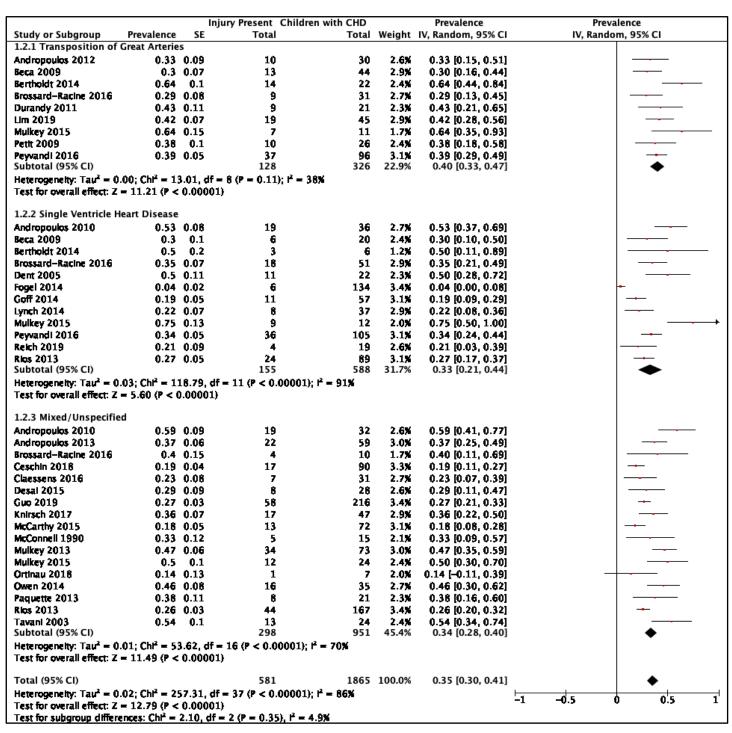


Figure 4. Postoperative Prevalence of Brain Injuries in Children with Congenital Heart Disease.

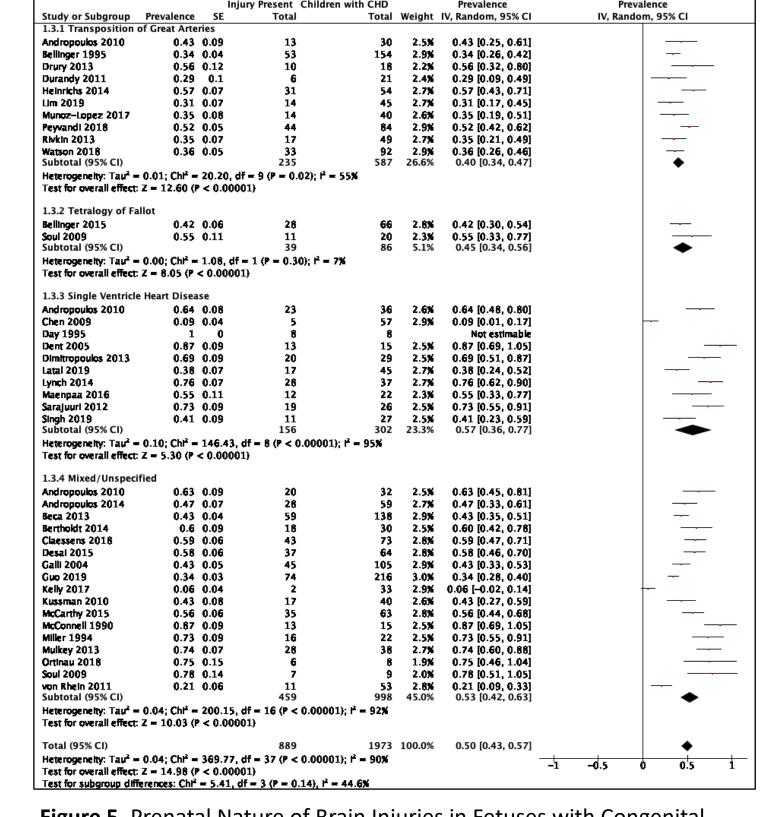


Figure 5. Prenatal Nature of Brain Injuries in Fetuses with Congenital Heart Disease.

| Study or Subgroup | Prevalence | SE | Total | Total | Weight | IV, Random, 95% C | I IV, Random, 95% CI |
|---|---------------|--------------|---|-----------|---------|--------------------|----------------------|
| 2.1.1 Ventriculomegaly | , | | | | | | |
| Arroyo 2019 | 0.12 | 0.03 | 11 | 94 | 26.7% | 0.12 [0.06, 0.18] |] - |
| Brossard-Racine 2014 | 0.09 | 0.02 | 13 | 144 | 34.6% | 0.09 [0.05, 0.13] |] + |
| Griffiths 2019 | 0.25 | 0.11 | 4 | 16 | 4.4% | 0.25 [0.03, 0.47] |] |
| Miczoch 2013 | 0.04 | 0.03 | 2 | 53 | 26.7% | 0.04 [-0.02, 0.10] |] + |
| Schellen 2015 | 0.21 | 0.08 | 5 | 24 | 7.6% | 0.21 [0.05, 0.37] |] |
| Subtotal (95% CI) | | | 35 | 331 | 100.0% | 0.10 [0.05, 0.15 | 1 ♦ |
| Heterogeneity: Tau ² = 0 Test for overall effect: Z | | - | = 4 (P = 0.09); 1 ² = 51% } | | | | |
| 2.1.2 Hypoplasia of Ce | rebellar Verm | iis | | | | | |
| Brossard-Racine 2014 | 0.02 | 0.01 | 3 | 144 | 79.0% | 0.02 [0.00, 0.04] | 1 |
| Griffiths 2019 | 0.13 | 0.08 | 2 | 16 | 1.2% | | - |
| Mkzoch 2013 | 0.02 | 0.02 | 1 | 53 | 19.8% | | |
| Subtotal (95% CI) | | | 6 | 213 | 100.0% | 0.02 [0.00, 0.04 | j • |
| 2.1.3 Subependymal Cy Brossard-Racine 2014 Miczoch 2013 | 0.01 | 0.01 0.03 | 2 2 | 144 53 | | | - |
| Subtotal (95% CI) | 0.04 | 0.03 | 4 | | 100.0% | | |
| Heterogenelty: $Tau^2 = 0$ Test for overall effect: Z | | | $= 1 (P = 0.34); t^2 = 0\%$ | | | | |
| 2.1.4 Mixed | | | _ | | | | |
| Arroyo 2019 | | 0.04 | 73 | 94 | | | |
| Brossard-Racine 2014 | | 0.01 | 3 | 144 | | | |
| Mkzoch 2013 | 0.11 | 0.04 | 6 82 | 53 | | | |
| C 1 1 (0 Est C) | | | 87 | 291 | 100.0% | 0.30 [-0.13, 0.74 | |
| Subtotal (95% CI) | | | | | 100.070 | | |
| | | | $df = 2 (P < 0.00001); l^2 =$ | | 100.070 | | |
| Heterogeneity: $Tau^2 = 0$ | | | | | 100.0% | , | |

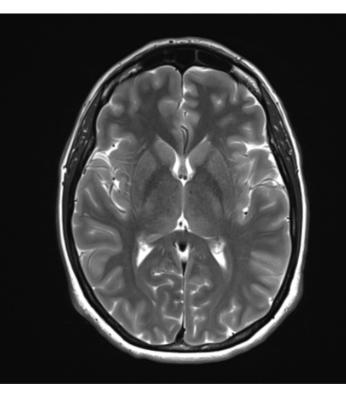
Figure 6. Postnatal-Preoperative Nature of Brain Injuries in Children with Congenital Heart Disease.

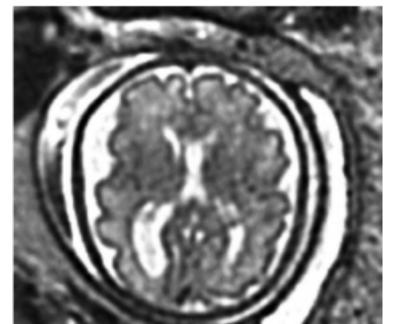
| tudy or Subgroup P .2.1 Ventriculomegaly | Injury revalence SE | Present Childre Total | | Prevalence ht IV, Random, 95% CI | Prevalence IV, Random, 95% CI |
|--|---------------------------------------|--------------------------|-------------------------------------|---|----------------------------------|
| nirsch 2017 | 0.04 0.03 | 2 | 47 26. | 6% 0.04 [-0.02, 0.10] | - |
| cConnell 1990 rtinau 2012 | 0.33 0.12 0.57 0.06 | 5 38 | 15 22. 67 25. | | |
| wen 2014 | 0.14 0.06 | 5 | 35 25. | 6% 0.14 [0.02, 0.26] | |
| btotal (95% CI) terogeneity: Tau² = 0.07 | | 50 (P < 0.00001); f² | 164 100.9 = 95% | 0.27 [0.00, 0.53] | |
| est for overall effect: Z = 1 | 99 (P = 0.05) | | | | |
| 2.2 White Matter Injury adropoulos 2010 | 0.37 0.06 | 25 | | 5% 0.37 [0.25, 0.49] | - |
| ndropoulos 2013 rossard-Racine 2016 | 0.29 0.06 0.23 0.04 | 17 24 | | 5% 0.29 [0.17, 0.41] 0% 0.23 [0.15, 0.31] | |
| laessens 2016 | 0.19 0.07 | -6 | | 5% 0.19 [0.05, 0.33] | |
| laessens 2019 | 0.34 0.05 | 34 | | 7% 0.34 [0.24, 0.44] | |
| ent 2005 esal 2015 | 0.36 0.1 0.29 0.09 | 6 6 | 22 3. 28 4. | 4% 0.36 [0.16, 0.56] 0% 0.29 [0.11, 0.47] | |
| urandy 2011 | 0.19 0.09 | 4 | 21 4. | 0.19 [0.01, 0.37] | |
| uo 2019 nirsch 2017 | 0.27 0.03 0.11 0.04 | 58 5 | 216 10. 47 9. | | |
| lulkey 2013 | 0.14 0.04 | 10 | 73 9. | | |
| lulkey 2015 Irtinau 2018 | 0.29 0.09 0.14 0.13 | 7 1 | 24 4. 7 2. | : | |
| wen 2014 | 0.2 0.07 | 7 | | 3% 0.14 [-0.11, 0.39] 5% 0.20 [0.06, 0.34] | |
| aquette 2013 | 0.38 0.11 | 8 | | 0.38 [0.16, 0.60] | |
| los 2013 ubtotal (95% CI) | 0.19 0.03 | 32 254 | 167 10. 1022 100. | | • |
| eterogeneity: $Tau^2 = 0.00$ est for overall effect: $Z = 1$ | | $(P = 0.003); t^2 =$ | - 57 % | | |
| 2.3 Increased Extra-Axia | | | | | |
| nirsch 2017 | 0.17 0.05 | 8 | 47 50. | | l l |
| rtinau 2012 ubtotal (95% CI) | 0.51 0.06 | 34 42 | 67 49. 114 100. | | |
| eterogeneity: $Tau^2 = 0.05$ | | _ | | | |
| est for overall effect: Z = 1 2.4 Ischemia | | | | | |
| laessens 2019 | 0.3 0.05 | 30 | 100 24. | | |
| ent 2005 nirsch 2017 | 0.18 0.08 0.04 0.03 | 4 2 | 22 18. 47 27. | | l l |
| eyvandi 2016 | 0.04 0.03 | 2 | 153 29. | W 0.01 [-0.01, 0.03] | • |
| ubtotal (95% CI) eterogeneity: Tau² = 0.01 | : Chi ² = 3.6 5.0 45 = 2 : | 38 (P < 0.00001): P | 322 100.0 = 92¥ | 0.12 [0.01, 0.23] | • |
| eterogeneity: Taur = 0.01 est for overall effect: Z = 2 | | , ~ v.vvv01); F | - 96A | | |
| .2.5 Hemorrhage | | . - | <u>-</u> - | | |
| ndropoulos 2010 ertholdt 2014 | 0.24 0.05 0.47 0.09 | 16 14 | | 0% 0.24 [0.14, 0.34] 5% 0.47 [0.29, 0.65] | l l |
| rossard-Racine 2016 | 0.11 0.03 | 11 | 103 8. | 6X 0.11 [0.05, 0.17] | - |
| laessens 2019 ent 2005 | 0.57 0.05 0.09 0.06 | 57 2 | | 0.57 [0.47, 0.67] | - |
| em 2005 Imitropoulos 2013 | 0.03 0.06 | 3 | | 7% 0.09 [-0.03, 0.21] 9% 0.03 [0.01, 0.05] | - |
| urandy 2011 | 0.24 0.09 | 5 | 21 6. | 5% 0.24 [0.06, 0.42] | _ - |
| ogel 2014 elly 2014 | 0.05 0.02 0.36 0.04 | 7 52 | | 8% 0.05 [0.01, 0.09] 8% 0.36 [0.28, 0.44] | <u> </u> |
| lahle 2002 | 0.04 0.04 | 1 | 24 8. | 3% 0.04 [- 0.04, 0.12] | + |
| luikey 2013 Irtinau 2018 | 0.27 0.05 0.14 0.13 | 20 1 | | 0% 0.27 [0.17, 0.37] 0% 0.14 [-0.11, 0.39] | |
| Wen 2014 | 0.14 0.13 0.26 0.07 | 9 | 35 7. | 3× 0.26 [0.12, 0.40] | - |
| ubtotal (95% CI) leterogenelty: Tau² = 0.02 | | 198 2 (P < 0.00001) | 880 100.9 ; 1 ² = 95% | 0.22 [0.13, 0.30] | • |
| est for overall effect: Z = 4 | | | | | |
| .2.6 Sinovenous Thromb Indropoulos 2010 | osis 0.03 0.02 | 2 | 68 50. | 0.03 [-0.01, 0.07] | |
| laessens 2019 | 0.04 0.02 | 4 | 100 50. | 0.04 [0.00, 0.08] | |
| ubtotal (95% CI) leterogenelty: Tau ² = 0 00 | · Chi ² = 0 12 -44 - 4 4- | 6 - 0 72): P = 0% | 168 100. | 0.04 [0.01, 0.06] | |
| leterogeneity: Tau² = 0.00 lest for overall effect: Z = 2 | | - v./2/; r = V% | ı | | |
| .2.7 Stroke | | | | | |
| ndropoulos 2013 | 0.1 0.04 | 6 | 59 12. | | |
| eca 2013 Iaessens 2016 | 0.05 0.02 0.1 0.05 | 7 3 | 147 17. 31 10. | | <u> </u> |
| laessens 2016 | 0.12 0.04 | 8 | 66 12. | 6% 0.12 [0.04, 0.20] | l l |
| nirsch 2017 Icht 2009 | 0.19 0.06 0.1 0.05 | 9 4 | 47 8. 42 10. | | |
| icit 2009 Im 2019 | 0.09 0.04 | 4 | 45 12. | 6X 0.09 [0.01, 0.17] | |
| eyvandi 201 6 ubtotal (95% CI) | 0.2 0.03 | 31 72 | 153 15. 590 100. | | |
| eterogeneity: $Tau^2 = 0.00$ | | _ | | 0.12 [0.07, 0.10] | \ |
| est for overall effect: Z = 5 | .vo (r < 0.00001) | | | | |
| .2.8 Infarct ndropoulos 2010 | 0.18 0.05 | 12 | 68 10. | % 0.18 [0.08, 0.28] | |
| rossard-Racine 2016 | 0.03 0.02 | 3 | 103 11. | 6% 0.03 [-0.01, 0.07] | - |
| urandy 2011 Iahle 2002 | 0.19 0.09 0.08 0.06 | 4 2 | 21 8. 24 9. | | l l |
| ianie 2002 IcConnell 1990 | 0.07 0.06 | 1 | 15 9. | 8% 0.07 [-0.05, 0.19] | |
| lulkey 2013 lulkey 2015 | 0.66 0.06 | 48 | 73 9. 24 8 | 8% 0.66 [0.54, 0.78] | - |
| lulkey 2015 Wen 2014 | 0.25 0.09 0.09 0.05 | 6 3 | 24 8. 35 10. | 1% 0.25 [0.07, 0.43] 4% 0.09 [-0.01, 0.19] | |
| artridge 2006 | 0.09 0.05 | 3 | 32 10. | × 0.09 [-0.01, 0.19] | |
| los 2013 ubtotal (95% CI) | 0.1 0.02 | 1 6 98 | 167 11. 562 100. | | → |
| eterogeneity: $Tau^2 = 0.02$ est for overall effect: $Z = 3$ | • • • • • • • • • | (P < 0.00001); | r = 92% | | |
| 2.9 Periventricular Leuk | | | | | |
| ent 2005 | 0.05 0.04 | 1 | 22 20. | | |
| off 2014 meh 2014 | 0.19 0.05 | 11 8 | 57 16. 37 11 | | I |
| ynch 2014 Iahle 2002 | 0.22 0.07 0.17 0.08 | 8 4 | 37 11. 24 9. | | |
| cCarthy 2015 | 0.18 0.05 | 13 | 72 16. | 0.18 [0.08, 0.28] | |
| ulkey 2013 ubtotal (95% CI) | 0.08 0.03 | 6 43 | 73 24. 285 100.0 | | |
| eterogeneity: $Tau^2 = 0.00$ est for overall effect: $Z = 4$ | | $(P = 0.06); l^2 = 5$ | | · | |
| .2.10 Mixed | | | | | |
| .2.10 Mixed rossard-Racine 2016 | 0.09 0.03 | 9 | 103 18. | 3% 0.09 [0.03, 0.15] | - |
| eschin 2018 | 0.19 0.04 | 17 | 90 17. | 9X 0.19 [0.11, 0.27] | - |
| | 0.4 0.1 0.14 0.04 | 10 10 | 25 14. 73 17. | | |
| | 0.33 0.1 | 8 | 24 14. | 5X 0.33 [0.13, 0.53] | |
| icht 2004 Iulkey 2013 Iulkey 2015 | 0.64 0.06 | 43 97 | 67 17. 382 100. | | |
| lulkey 2013 lulkey 2015 Irtinau 2012 | **** | | | [UITJ] | |
| ulkey 2013 ulkey 2015 rtinau 2012 ubtotal (95% CI) eterogeneity: Tau ² = 0.03 | ; Chi² = 75.18, df = 5 | _ | | | |
| ulkey 2013 ulkey 2015 rtinau 2012 ubtotal (95% CI) | ; Chi² = 75.18, df = 5 | _ | | | |
| ilkey 2013 ilkey 2015 tinau 2012 btotal (95% CI) iterogenelty: Tau ² = 0.03 | ; Chi² = 75.18, df = 5 | _ | | | -1 -0.5 0 0.5 1 |

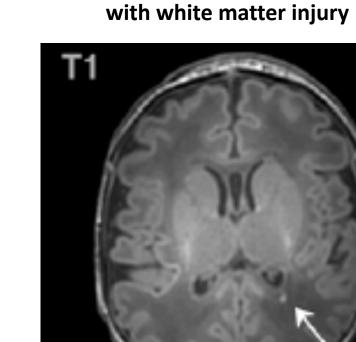
Figure 7. Postoperative Nature of Brain Injuries in Children with Congenital Heart Disease.

| 2.3.1 Ventriculomegal | Prevalence SE y | ry Present Childre Total | | Weight | Prevalence IV, Random, 95% CI | Prevalence IV, Random, 959 |
|--|--|--|--|--|---|-------------------------------|
| Bellinger 2015 Latal 2019 | 0.02 0.02 0.22 0.06 | 1 10 | 66 46 | 18.3% 15.6% | 0.02 [-0.02, 0.06] 0.22 [0.10, 0.34] | + |
| McConnell 1990 | 0.73 0.11 | 11 | 15 | 11.2% | 0.73 [0.51, 0.95] | _ |
| Miller 1994 Ortinau 2016 | 0.18 0.08 0.38 0.17 | 4 3 | 22 8 | 13.6% 7.2% | 0.18 [0.02, 0.34] 0.38 [0.05, 0.71] | |
| Salama 2016 | 0.28 0.06 | 14 | 50 | 15.6% | 0.28 [0.16, 0.40] | |
| Soul 2009 Subtotal (95% CI) | 0.02 0.02 | 1 44 | 48 255 | 18.3% 100.0% | 0.02 [-0.02, 0.06] 0.22 [0.11, 0.33] | † ◆ |
| Heterogeneity: Tau ² = (Test for overall effect: 2 | | = 6 (P < 0.00001); | i ² = 92% | | | |
| 2.3.2 White Matter Inju | шгу | | | | | |
| Andropoulos 2010 | 0.46 0.06 | 31 17 | 66 | 5.4% | 0.46 [0.34, 0.58] | _ |
| Andropoulos 2013 Beca 2013 | 0.29 0.06 0.41 0.04 | 57 | 59 138 | 5.4% 5.7% | 0.29 [0.17, 0.41] 0.41 [0.33, 0.49] | - |
| Bellinger 1995 | 0.03 0.01 0.02 0.02 | 4 1 | 142 | 6.0% | 0.03 [0.01, 0.05] | <u>t</u> |
| Bellinger 2015 Bertholdt 2014 | 0.02 0.02 | 6 | 66 30 | 5.9% 5.3% | 0.02 [-0.02, 0.06] 0.20 [0.06, 0.34] | T |
| Claessens 2018 | 0.65 0.08 | 26 | 40 | 5.1% | 0.65 [0.49, 0.81] | |
| Claessens 2019 Day 1995 | 0.48 0.04 0.63 0.17 | 60 5 | 124 8 | 5.7% 3.3% | 0.48 [0.40, 0.56] 0.63 [0.30, 0.96] | |
| Desai 2015 | 0.58 0.06 | 37 | 64 | 5.4% | 0.58 [0.46, 0.70] | |
| Durandy 2011 Guo 2019 | 0.1 0.06 0.34 0.03 | 2 74 | 21 21 6 | 5.4% 5.8% | 0.10 [-0.02, 0.22] 0.34 [0.28, 0.40] | |
| Heinrichs 2014 | 0.19 0.05 | 10 | 54 | 5.6% | 0.19 [0.09, 0.29] | |
| Latal 2019 Miller 1994 | 0.11 0.05 0.41 0.1 | 5 9 | 45 22 | 5.6% 4.7% | 0.11 [0.01, 0.21] 0.41 [0.21, 0.61] | |
| Ortinau 2016 Salama 2016 | 0.5 0.18 0.38 0.07 | 4 19 | 8 50 | 3.2% 5.3% | 0.50 [0.15, 0.85] 0.38 [0.24, 0.52] | |
| Singh 2019 | 0.11 0.06 | 3 | 27 | 5.4% | | - |
| von Rhein 2011 Subtotal (95% CI) | 0.11 0.04 | 6 376 | 53 1235 | 5.7% 100.0% | 0.11 [0.03, 0.19] 0.30 [0.21, 0.39] | |
| Heterogeneity: Tau ² = (Test for overall effect: 2 | | | 1); f² = 96% | | | |
| 2.3.3 Ischemia | | | | | | |
| Claessens 2019 Dent 2005 | 0.41 0.04 0.4 0.13 | 51 6 | 124 15 | 26.9% 22.0% | 0.41 [0.33, 0.49] 0.40 [0.15, 0.65] | _ |
| Latal 2019 | 0.04 0.03 | 2 | 45 | 27.1% | 0.04 [-0.02, 0.10] | + |
| Sarajuuri 2012 Subtotal (95% CI) | 0.58 0.1 | 15 74 | 2 6 210 | 24.0% 100.0% | 0.58 [0.38, 0.78] 0.35 [0.08, 0.62] | - |
| Heterogeneity: $Tau^2 = 0$ | | | | | | |
| Test for overall effect: 2 | z = 2.55 (P = 0.01) | | | | | |
| 2.3.4 Hemorrhage | 0.20 0.25 | 10 | | m Art | 0.20 (0.40 0.20 | |
| Andropoulos 2010 Andropoulos 2013 | 0.28 0.05 0.17 0.05 | 19 10 | 68 59 | 7.8% 7.8% | 0.28 [0.18, 0.38] 0.17 [0.07, 0.27] | |
| Bertholdt 2014 | 0.67 0.09 | 20 | 30 | 6.7% | 0.67 [0.49, 0.85] | |
| Claessens 2019 Dent 2005 | 0.17 0.03 0.53 0.13 | 21 8 | 124 15 | 8.2% 5.4% | 0.17 [0.11, 0.23] 0.53 [0.28, 0.78] | - |
| Dimitropoulos 2013 | 0.02 0.01 | 2 | 104 | 8.4% | 0.02 [0.00, 0.04] | <u> </u> |
| Durandy 2011 Kelly 2014 | 0.14 0.08 0.43 0.04 | 3 59 | 21 138 | 7.0% 8.0% | 0.14 [-0.02, 0.30] 0.43 [0.35, 0.51] | - |
| Mahle 2002 McConnell 1990 | 0.43 0.11 0.27 0.11 | 9 | 21 15 | 6.0% 6.0% | 0.43 [0.21, 0.65] | |
| Mulkey 2013 | 0.39 0.08 | 15 | 38 | 7.0% | 0.27 [0.05, 0.49] 0.39 [0.23, 0.55] | - |
| Ortinau 2016 Sarajuuri 2012 | 0.13 0.12 0.08 0.05 | 1 2 | 8 26 | 5.7% 7.8% | | |
| Singh 2019 | 0.04 0.04 | 1 | 27 | 8.0% | 0.04 [-0.04, 0.12] | + _ |
| Subtotal (95% CI) Heterogenelty: Tau² = (| 0.03; Chi ² = 225 A0 A | 174 f = 13 (P < 0.0000 | | 100.0% | 0.25 [0.16, 0.35] | ◀ |
| 2.3.5 Sinovenous Thro Andropoulos 2010 Claessens 2019 Subtotal (95% CI) | 0.1 0.04 0.1 0.03 | 7 12 19 | 68 124 192 | 36.0% 64.0% 100.0% | 0.10 [0.02, 0.18] 0.10 [0.04, 0.16] 0.10 [0.05, 0.15] | - |
| Heterogeneity: $Tau^2 = 0$ | | | | | , 0.20] | |
| Test for overall effect: 2 | t = 4.17 (P < 0.0001) | | | | | |
| 2.3.6 Stroke | | | | | | |
| Beca 2013 Bertholdt 2014 | 0.04 0.02 0.1 0.05 | 5 3 | 138 30 | 13.5% 8.6% | 0.04 [0.00, 0.08] 0.10 [0.00, 0.20] | <u>+</u> |
| Chen 2009 | 0.1 0.03 | 12 | 122 | 12.0% | 0.10 [0.04, 0.16] | - |
| Claessens 2016 Kelly 2017 | 0.19 0.05 0.06 0.04 | 14 2 | 73 33 | 8.8% 10.4% | 0.19 [0.09, 0.29] 0.06 [-0.02, 0.14] | - |
| Kussman 2010 Lim 2019 | 0.03 0.02 0.09 0.04 | 1 4 | 40 45 | 13.5% 10.4% | 0.03 [-0.01, 0.07] 0.09 [0.01, 0.17] | - |
| Peyvandi 2018 | 0.26 0.04 | 27 | 104 | 10.4% | 0.26 [0.18, 0.34] | · |
| von Rhein 2011 Subtotal (95% CI) | 0.04 0.03 | 2 70 | 53 638 | 12.0% 100.0% | 0.04 [-0.02, 0.10] 0.09 [0.05, 0.14] | † |
| Heterogenetty: Tau ² = (| | | 3 | | | |
| Test for overall effect: 2 | 0.00; $Chi^2 = 37.23$, df $Z = 4.09$ (P < 0.0001) | = 8 (P < 0.0001); | r = 79% | | | |
| | | = 8 (P < 0.0001); | r = 79% | | | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 | Z = 4.09 (P < 0.0001) 0.32 0.06 | 22 | 68 | 6.5% | 0.32 [0.20, 0.44] | _ |
| Test for overall effect: 2 2.3.7 Infarct | Z = 4.09 (P < 0.0001) | | | 6.5% 7.5% 8.3% | 0.32 [0.20, 0.44] 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 | 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 | 22 8 7 4 | 68 59 111 66 | 7.5% 8.3% 8.0% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 | 0.32 0.06 0.14 0.04 0.06 0.02 | 22 8 7 | 68 59 111 | 7.5% 8.3% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 | Z = 4.09 (P < 0.0001) 0.32 | 22 8 7 4 6 7 | 68 59 111 66 40 8 15 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2016 Day 1995 | 2 = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.86 0.12 | 22 6 7 4 6 7 1 1 9 | 68 59 111 66 40 8 | 7.5% 8.3% 8.0% 6.5% 3.7% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2016 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 | Z = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.88 0.12 0.07 0.06 0.05 0.05 0.2 0.06 0.24 0.09 | 22 8 7 4 8 7 1 1 9 5 | 68 59 111 66 40 8 15 21 45 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 | Z = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.88 0.12 0.07 0.06 0.05 0.05 0.2 0.06 0.24 0.09 0.07 0.06 0.18 0.08 | 22 6 7 4 6 7 1 1 9 5 | 68 59 111 66 40 8 15 21 45 21 15 22 | 7.5% 6.3% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 5.4% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2016 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2018 | Z = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.88 0.12 0.07 0.06 0.05 0.05 0.2 0.06 0.24 0.09 0.07 0.06 0.18 0.08 0.25 0.15 | 22 6 7 4 8 7 1 1 9 5 1 4 2 | 68 59 111 66 40 8 15 21 45 21 15 22 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 5.4% 2.8% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] 0.25 [-0.04, 0.54] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 Miller 1994 Ortinau 2018 Partridge 2006 Salama 2016 | Z = 4.09 (P < 0.0001) 0.32 | 22 8 7 4 8 7 1 1 9 5 1 4 2 1 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 2.8% 7.5% 6.5% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.68 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.16 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.36] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2016 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2016 Partridge 2006 Salama 2016 Singh 2019 | Z = 4.09 (P < 0.0001) 0.32 | 22 8 7 4 8 7 1 1 9 5 1 4 2 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 50 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 5.4% 2.6% 7.5% 6.5% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.38] 0.15 [0.01, 0.29] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2018 Partridge 2006 Salama 2016 Singh 2019 Subtotal (95% CI) Heterogeneity: Tau² = 6 | Z = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.86 0.12 0.07 0.06 0.05 0.05 0.2 0.06 0.24 0.09 0.07 0.06 0.18 0.08 0.25 0.15 0.04 0.04 0.26 0.06 0.15 0.07 0.01; Chi² = 83.20, df | 22 8 7 4 8 7 1 1 9 5 1 4 2 1 13 4 97 - 15 (P < 0.00001 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 50 27 601 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 2.8% 7.5% 6.5% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.68 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.16 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.36] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2018 Partridge 2006 Salama 2016 Singh 2019 Subtotal (95% CI) Heterogenetty: Tau² = 6 Test for overall effect: 2 | Z = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.88 0.12 0.07 0.06 0.05 0.25 0.2 0.06 0.24 0.09 0.07 0.06 0.18 0.08 0.25 0.15 0.04 0.04 0.26 0.06 0.15 0.07 0.01; Chi² = 83.20, df Z = 5.55 (P < 0.00001 | 22 8 7 4 6 7 1 1 9 5 1 4 2 1 13 4 97 = 15 (P < 0.00001 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 50 27 601 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 5.4% 2.6% 7.5% 6.5% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.38] 0.15 [0.01, 0.29] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2016 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2016 Partridge 2006 Salama 2016 Singh 2019 Subtotal (95% CI) Heterogeneity: Tau² = 6 Test for overall effect: 2 2.3.8 Brain Mineralizat | 2 = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.88 0.12 0.07 0.06 0.05 0.05 0.2 0.06 0.24 0.09 0.07 0.06 0.18 0.08 0.25 0.15 0.04 0.04 0.26 0.06 0.15 0.07 0.01; Chi² = 83.20, df 2 = 5.55 (P < 0.00001 tion/Hemosiderin Dej | 22 8 7 4 8 7 1 1 9 5 1 4 2 1 13 4 97 = 15 (P < 0.00001 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 50 27 601 3; 1 ² = 82% | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 4.9% 6.5% 5.4% 2.8% 7.5% 6.5% 5.9% 100.0% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.38] 0.15 [0.01, 0.29] 0.17 [0.11, 0.23] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2018 Partridge 2006 Salama 2016 Singh 2019 Subtotal (95% CI) Heterogenetty: Tau² = 6 Test for overall effect: 2 | Z = 4.09 (P < 0.0001) 0.32 0.06 0.14 0.04 0.06 0.02 0.06 0.03 0.2 0.06 0.88 0.12 0.07 0.06 0.05 0.25 0.2 0.06 0.24 0.09 0.07 0.06 0.18 0.08 0.25 0.15 0.04 0.04 0.26 0.06 0.15 0.07 0.01; Chi² = 83.20, df Z = 5.55 (P < 0.00001 | 22 8 7 4 6 7 1 1 9 5 1 4 2 1 13 4 97 = 15 (P < 0.00001 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 50 27 601 | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 4.9% 6.5% 5.4% 2.6% 7.5% 6.5% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.38] 0.15 [0.01, 0.29] | |
| Test for overall effect: 2 2.3.7 Infarct Andropoulos 2010 Andropoulos 2013 Bellinger 2011 Bellinger 2015 Claessens 2018 Day 1995 Dent 2005 Durandy 2011 Latal 2019 Mahle 2002 McConnell 1990 Miller 1994 Ortinau 2018 Partridge 2006 Salama 2016 Singh 2019 Subtotal (95% CI) Heterogenelty: Tau² = (Test for overall effect: 2 2.3.8 Brain Mineralizat Bellinger 2015 Kussman 2010 Watson 2016 | Z = 4.09 (P < 0.0001) 0.32 | 22 8 7 4 6 7 1 1 9 5 1 4 2 1 13 4 97 = 15 (P < 0.00001) posit 21 14 22 | 68 59 111 66 40 8 15 21 45 21 15 22 8 25 50 27 601 3; 12 = 82% | 7.5% 8.3% 8.0% 6.5% 3.7% 6.5% 7.0% 6.5% 5.4% 2.8% 7.5% 6.5% 5.9% 100.0% | 0.14 [0.06, 0.22] 0.06 [0.02, 0.10] 0.06 [0.00, 0.12] 0.20 [0.08, 0.32] 0.88 [0.64, 1.12] 0.07 [-0.05, 0.19] 0.05 [-0.05, 0.15] 0.20 [0.08, 0.32] 0.24 [0.06, 0.42] 0.07 [-0.05, 0.19] 0.18 [0.02, 0.34] 0.25 [-0.04, 0.54] 0.04 [-0.04, 0.12] 0.26 [0.14, 0.38] 0.15 [0.01, 0.29] 0.17 [0.11, 0.23] 0.32 [0.20, 0.44] 0.35 [0.19, 0.51] 0.24 [0.16, 0.32] | |
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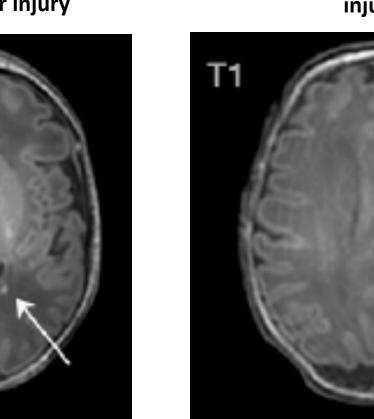








T1 MRI of 6-week, TGA neonate



T1 MRI of 5-week, Pulmonary

atresia neonate with white matter

CONCLUSION

- Brain injuries are prevalent in more than a fifth of children with CHD across both prenatal and postnatal periods.
- > A further increase is evident postoperatively, indicating the adverse impact of surgical intervention on brain outcomes.







A Systematic Review of Contemporary Methods in Patellofemoral Joint Radiography and Grading of Patellofemoral Osteoarthritis

Jonathan R. Hill 1,2, Edwin H.G. Oei 3, Kay M. Crossley 4, Hylton B. Menz 4, Erin M. Macri 3, Michelle D. Smith 1, Narelle Wyndow 4, Liam Maclachlan 1, Megan Ross 1, Natalie J. Collins 1 ¹The University of Queensland, Brisbane, Australia ²Ochsner Clinical School, New Orleans, USA ³ Erasmus MC University Medical Center, Rotterdam, Netherlands ⁴La Trobe University, Melbourne, Australia

BACKGROUND

- The patellofemoral joint (PFJ) is the most commonly affected compartment in knee osteoarthritis (OA)¹
- Radiographs are the most widely used imaging modality in OA evaluation²
- Radiographs are the only modality accepted by the FDA for assessment of OA structural change³
- Lack of standardized PFJ radiograph acquistion techniques result in variances in patient positioning, weight-bearing status, flexion angle, and beam direction⁴
- No current consensus exists for optimal methods of radiographic grading of patellofemoral osteoarthritis (PFOA) or optimal radiographic measures and thresholds for PFJ alignment⁵

To conduct a systematic review of the literature published since January 2000 to:

- 1) provide an overview of contemporary methods of acquiring radiographs of the PFJ
- 3) summarize PFJ alignment and bony morphology measures as identified on radiography

2) describe current methods of radiographic grading of PFOA and their measurement properties

METHODS

search strategy

- 1) "X-Rays"[MeSH] OR xray* OR x-ray* OR "plain film*" OR radiograph* OR radiolog* OR radiogram* OR roentgenograph* OR roentgenogram* OR "Radiography" [MeSH] OR sunrise OR merchant OR skyline OR axial OR lateral OR laurin OR tangential
- 2) "Patella"[mh] OR Patell* OR "Patellofemoral Joint"[mh] OR "anterior knee" OR PFJ OR PF OR "knee cap*" OR kneecap* OR (anterior[Title/Abstract] AND knee[Title/Abstract])
- 3) 1 AND 2

inclusion criteria

mention radiography of PFJ, anterior knee, or patella describe radiography acquisition technique

databases searched

PubMed CINAHL **SPORTDiscus** SCOPUS **EMBASE** PsycInfo **CENTRAL**

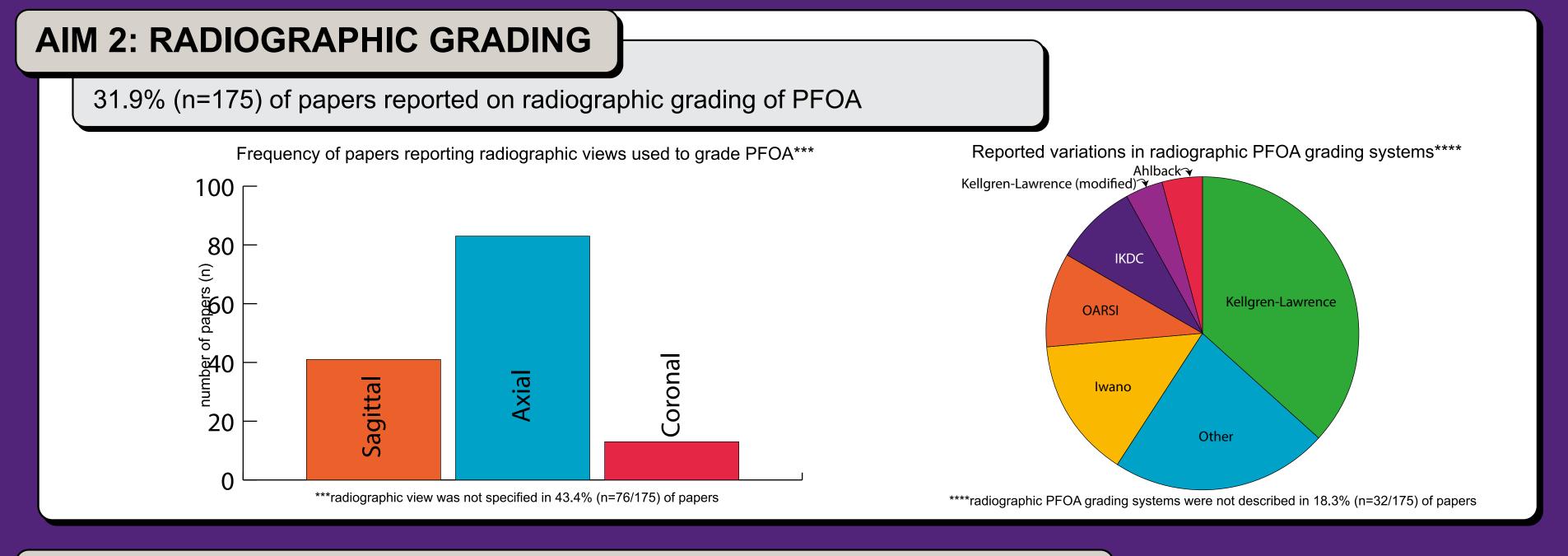
Web of Science

exclusion criteria

non-human participants cadaveric studies mean age <10 years single-subject studies non-English studies published before 2000

PRISMA flowchart 18,678 database search 3,625 duplicates removed 15,053 title & abstract 9,962 excluded 5,091 4,542 549

AIM 1: RADIOGRAPHIC METHODS 100% (n=549) of papers reported on methods of acquiring radiographs of the PFJ Reported variations in description of axial radiographs of PFJ Frequency of papers reporting radiographic views of the PFJ Clinical (n=314) flexion angle was not specified in 71.7% (n=332/463) of papers Sagittal Lower-Limb Alignment Reported variations in acquisition of axial radiographs of PF Research (n=235) Sagittal Lower-Limb Alignment 150 200 250 300 veightbearing status was not specified in 83.0% (n=322/388) of papers



AIM 3: RADIOGRAPHIC ALIGNMENT/MORPHOLOGY MEASURES

67.4% (n=370) of papers reported on radiographic PFJ alignment and/or morphology measures

SUMMARY

Preliminary findings suggest:

- 4 primary radiographic views (coronal, sagittal, axial, and lower-limb alignment) are used to acquire radiographs of the PFJ
- many variations exist in acquiring these views, including weightbearing status and knee flexion angle
- these variations potentially impact the outcomes of OA grading systems
- a number of different radiographic grading systems are used to assess the severity of PFOA

These findings illustrate the need for clear guidelines to be developed for consistency in the way that PFJ radiographs are acquired and graded











¹Duncan RC et al. (2006). Rheumatology. 45:757-60. ²Buckland-Wright JC (1994). Ann Rheum Dis. 53:268-75. ³Guermazi A et al. (2009). J Bone Joint Surg Am. 91 Suppl 1():54-62. ⁴Lankhorst NE et al. (2017). Osteoarthritis Cartilage. 25:647-53.

Incidental Findings in the Emergency Department

Mary Kassis, University of Queensland MD – 44557357

Supervisors: Dr Rob Eley, University of Queensland Faculty of Medicine and Princess Alexandra Hospital – Emergency Department Dr Georgia Livesay, University of Queensland Faculty of Medicine and Princess Alexandra Hospital – Emergency Department

Introduction

Medical imaging is used by clinicians to aid in diagnoses of presenting complaints. Emerging technologies with greater sensitivity result in increasing numbers of findings that do not relate to the main purpose of the investigation. These incidental findings, also known as incidentalomas, raise questions regarding the required communication between patient and clinician and subsequent follow-up.



Figure 1. Trauma computed tomography scan showing an incidental liver mass (arrow) in an elderly male.

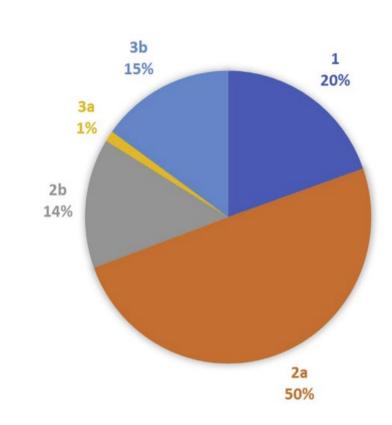


Figure 2. Classification and distribution of Incidental findings. Class 1 findings are benign anatomic variants that require no form of intervention. Class 2a findings are benign pathologic findings not requiring additional investigation based on the known natural histories of these lesions. Class 2b findings are likely benign and pathologic, and may require outpatient monitoring. Class 3a findings are pathologic findings requiring attention before discharge. Class 3b findings are pathologic findings requiring outpatient follow-up.

Methods

Key terms were searched in multiple databases to identify papers and studies that were conducted about incidental findings in the emergency department. Studies were limited to papers published in English during 2000-2020 using the key words: incidental findings; emergency department; documentation; computed tomography OR radiograph or x-ray OR ultrasound OR MR).

Results

30 research papers came from four countries including one from Australia.

Incidental findings were reported in 4-62% of patients who underwent different medical imaging, with the majority resulting from CT scans, especially those of the abdomen and pelvis.

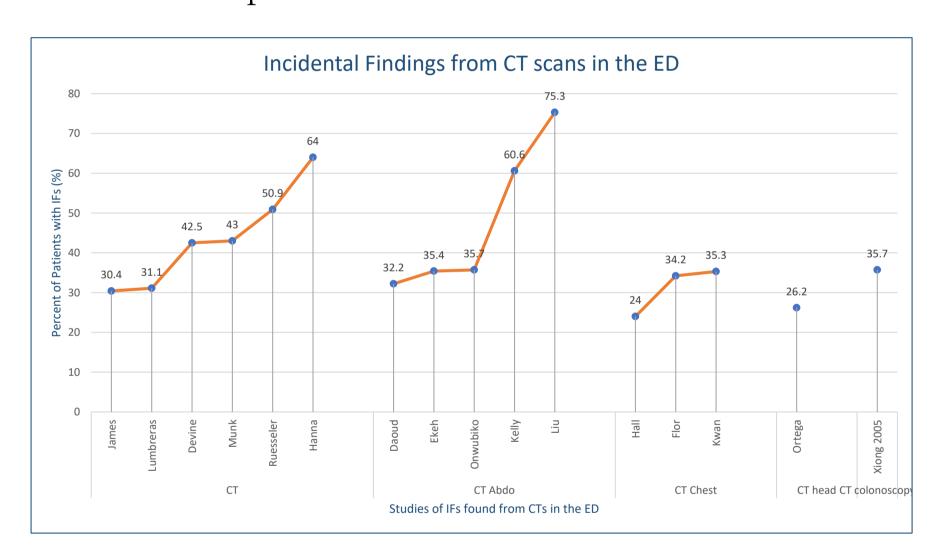


Figure 3. Incidental findings rates on computed tomography found in different studies.

A rate range between 17-51% of incidental findings was found in CT, with lower rates in x-ray and ultrasound.

Concerningly, low rates were reported in patient documentation (23-48%) and discharge summaries (10-25%) and in communication with patients about the findings (9-22%).

Discussion

Results showed increasing rate of incidental findings but low rates of reporting and communication.

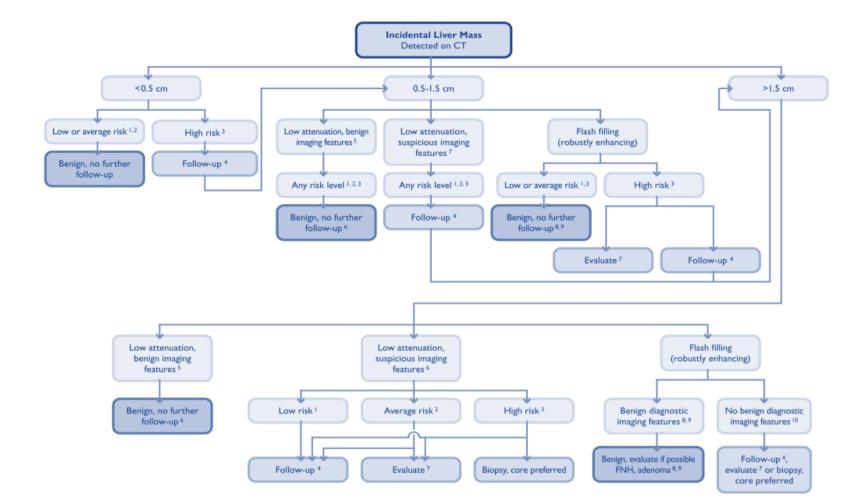
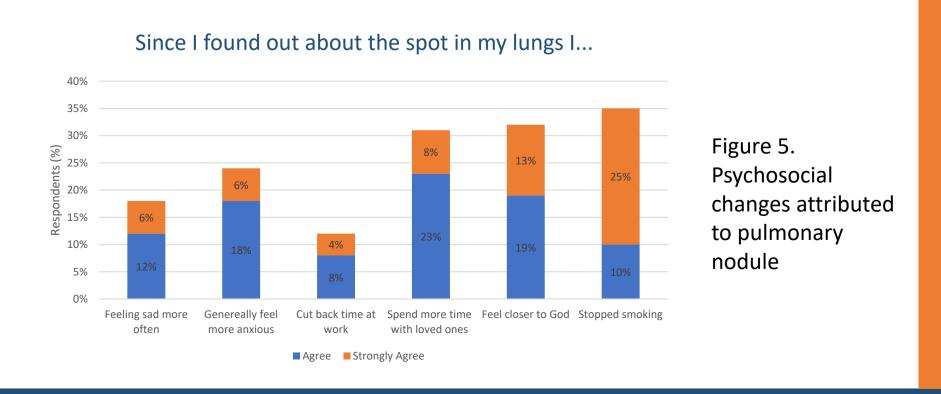


Figure 4. Flowchart for incidental liver mass detected on CT derived from expert consensus.

The studies illustrate that the potential benefit of discovering incidental findings that will lead to a change in management has to be weighed against the potential harm:

- Increase anxiety to patients
- Longer hospital stays
- Higher cost to patient and the system
- Further imaging risks (anaphylaxis, radiation exposure)



Figures References

- 1. Ekeh, A. P., et al. (2010). "The prevalence of incidental findings on abdominal computed tomography scans of trauma patients." Journal of Emergency Medicine 38(4): 484-489.
- 2. Philip, A., et al. (2017). "Incidental findings on pediatric abdominal computed tomography at a pediatric trauma center." Annals of Emergency Medicine 70(4): S87-S88.
- 3. Berland, L. L., et al. (2010). "Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee." Journal of the American College of Radiology 7(10): 754-773.

 4. Freiman, M. R., et al. (2016). "Patients' knowledge, beliefs, and distress associated with detection and evaluation of incidental pulmonary nodules for cancer: results from a multicenter survey." Journal of Thoracic Oncology 11(5): 700-708.

Adverse events during colchicine use: a systematic review and meta-analysis of randomized controlled trial events

S Stewart¹, Chih Kai Yang², Kate Atkins¹, Nicola Dalbeth¹, Philip Robinson²

¹Department of Medicine, University of Auckland, New Zealand; ²Faculty of Medicine, University of Queensland, Australia

Background

- . Colchicine is an anti-inflammatory agent which is widely used for the treatment of gout and also used extensively for familial Mediterranean fever, Behcet's disease and pericarditis.
- . The aim of the study was to systematically examine the adverse event (AE) profile of colchicine in randomized controlled trials (RCTs) across all published indications.

Methods

- . Systemic search using Cochrane, MEDLINE and EMBASE
- . Screened 4915 studies and included 35 RCT double blind studies
- . AE data were extracted by two independent reviewers under pre-defined categories: diarrhoea, gastrointestinal events (including diarrhoea), liver events, hematology events, muscle events, sensory events, infection events and death, and any AE
- . Meta-analysis were undertake to determine relative risk between colchicine group and comparator of adverse events

Results

- . 35 studies were included involving participants with cirrhosis (n=5), pericarditis (n=4), gout (n=5), knee osteoarthritis (n=3), Behcet's syndrome (n=3), psoriatic arthritis (n-2), post-pericardiotomy syndrome (n=2), and other (n=11)
- Any adverse events was reported in 21.1% of colchicine users compared to 18.9% in comparator groups, with an estimated risk ratio (RR)(95% confidence interval (CI)) of 1.46 (1.20-1.77) (**Table 1**)
- . Subgroup meta-analysis showed no significant difference in RR of AE in colchicine users between placebo and active comparator groups (Figure 1), nor between different cumulative drug dosages (Figure 2), nor between different disease indications (Figure 3)
- . The RR (95% CI) of diarrhea in colchicine users compared to comparator groups is 2.44 (1.62-3.69), and for any gastrointestinal AE was 1.74 (1.32-2.30), both p<0.001 (**Table 1**).
- . The RR of all other AE (liver, muscle, haematology, sensory, infectious) compared to comparator groups were not statistically significant (**Table 1**)

Table 1. Meta-analysis results of pooled RR of AE between colchicine and comparator groups

| | N. studies | n/N, % (95% CI) participants | | Pooled risk ratio (95% CI) | I ² (P value) | Overall effect, Z (P value) ^a | |
|-------------------------------|------------|------------------------------|------------------------------|----------------------------|---------------------------|--|--|
| | | Colchicine | Comparator | | | | |
| Any event | 27 | 845/4007, 21.1% (19.9, 22.4) | 784/4152, 18.9% (17.7, 20.1) | 1.46 (1.20, 1.77) | 58% (< 0.001) | 3.82 (< 0.001) | |
| Diarrhoea | 19 | 420/3212, 17.9% (16.8, 19.1) | 262/3142, 13.1% (11.9, 14.3) | 2.44 (1.62, 3.69) | 58% (< 0.001) | 4.24 (< 0.001) | |
| Gastrointestinal ^b | 29 | 729/4131, 17.6% (16.5, 18.8) | 552/4213, 13.1% (12.1, 14.2) | 1.74 (1.32, 2.30) | 53% (< 0.001) | 3.94 (< 0.001) | |
| Liver | 13 | 22/1150, 1.9% (1.2, 2.8) | 15/1362, 1.1% (0.6, 1.8) | 1.61 (0.86, 3.02) | 0% (0.48) | 1.50 (0.13) | |
| Muscle ^c | 9 | 37/872, 4.2% (3.0, 5.7) | 29/869, 3.3% (2.3, 4.7) | 1.25 (0.80, 1.93) | 0% (0.69) | 0.98 (0.33) | |
| Haematology | 8 | 16/2878, 0.6% (0.3, 0.9) | 12/2893 0.4% (0.2, 0.7) | 1.34 (0.64, 2.82) | 0% (0.69) | 0.77 (0.44) | |
| Sensory ^d | 2 | 3/201, 1.5% (0.4, 4.0) | 2/190, 1.1% (0.2, 3.4) | 1.35 (0.27, 6.74) | 0% (0.58) | 0.37 (0.71) | |
| Infectious | 7 | 105/2763, 3.8% (3.1, 4.6) | 131/2997, 4.4% (3.7, 5.1) | 1.03 (0.70, 1.51) | 46% (0.09) | 0.13 (0.90) | |

^aBolded *P* values indicate a significant overall effect in the risk ratio for an adverse event between colchicine and comparator groups. ^bThe gastrointestinal category includes diarrhoea. ^cThe muscle category includes myalgia, muscle cramps, myotoxicity, muscle weakness and elevated CPK. No rhabdomyolysis was assessed or reported by any study. ^dThe sensory category includes dysthesia and paresthesia. No neuropathy was assessed or reported by any study

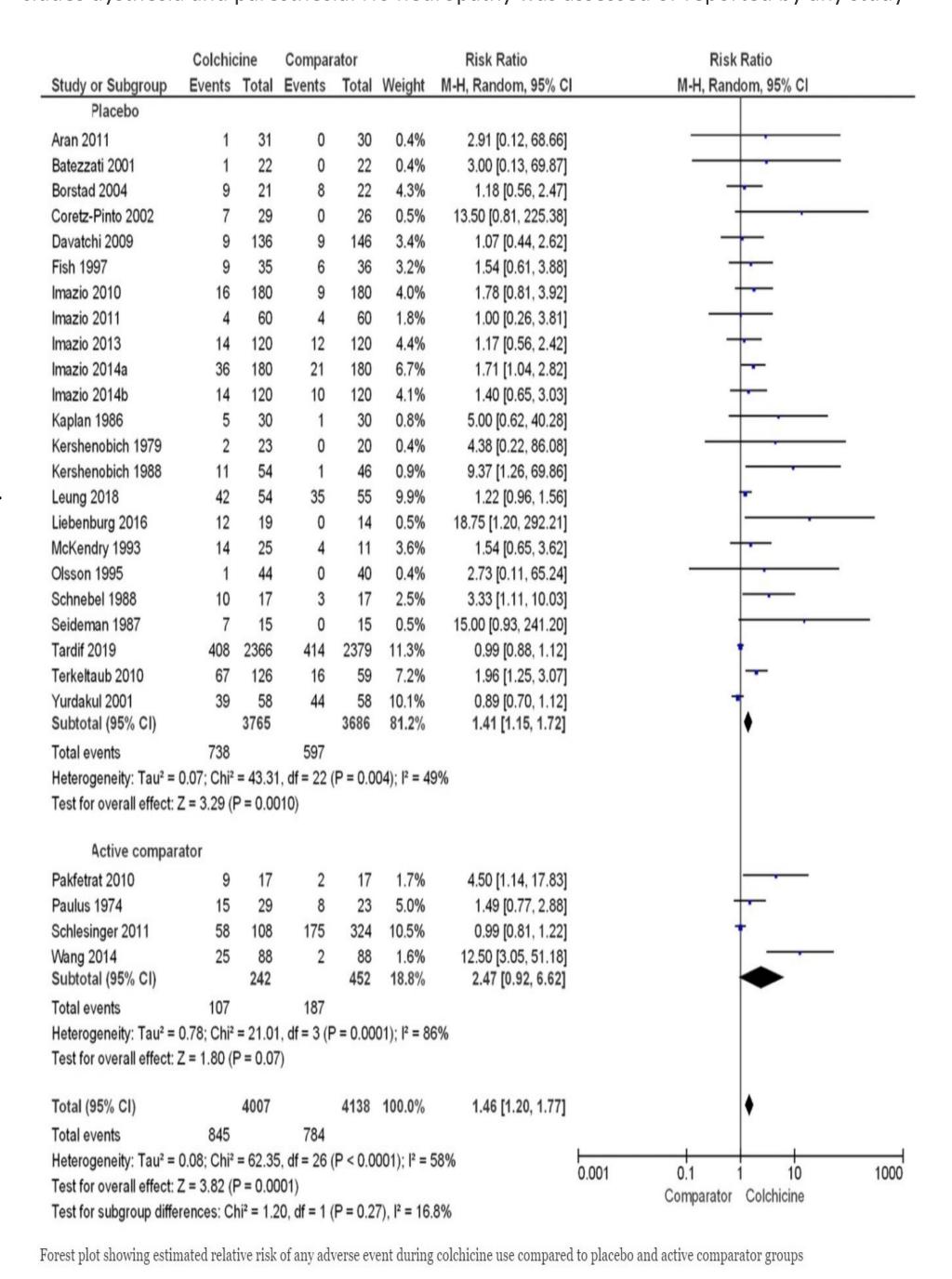


Figure 1. Forest plots showing estimated relative risk of any adverse event during colchicine use compared to placebo and active comparator groups

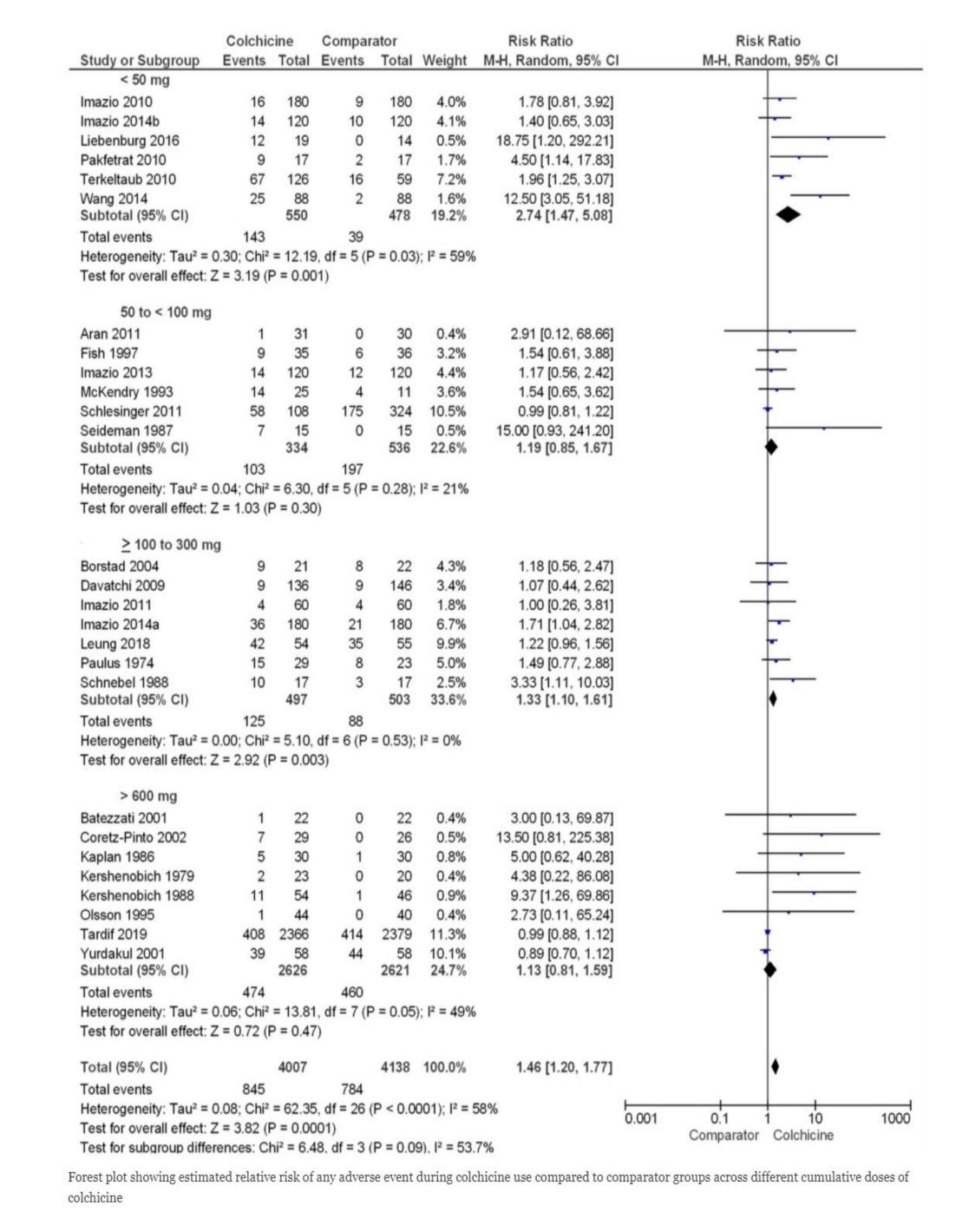


Figure 2. Forest plots showing estimated relative risk of any adverse event during colchicine use compared to comparator groups across different cumulative doses of colchicine

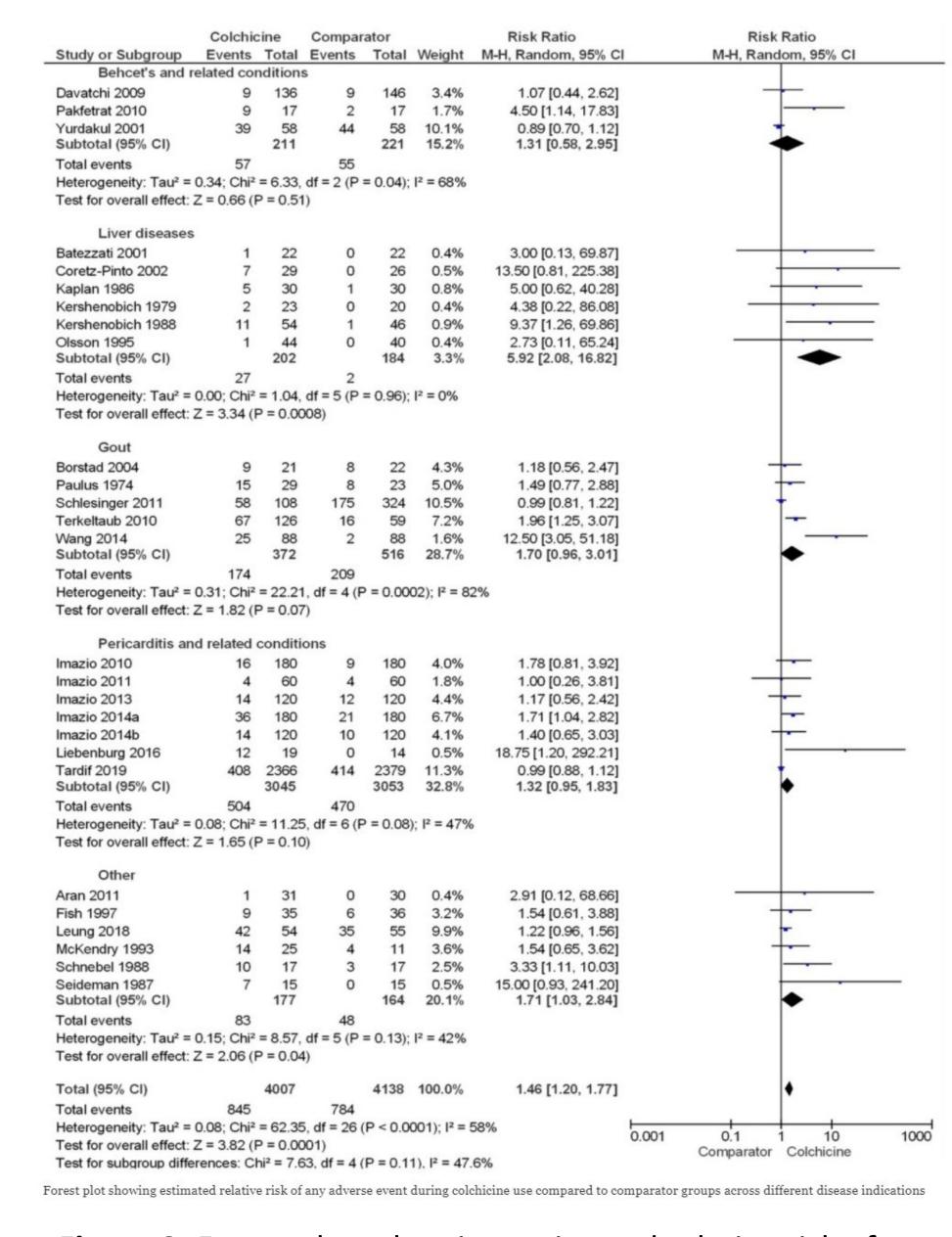


Figure 3. Forest plots showing estimated relative risk of any adverse event during colchicine use compared to comparator groups across different disease indications

Conclusion

This systematic review and meta-analysis provide reassurance that common adverse effects associated with colchicine are limited to diarrhoea and other gastrointestinal events. While these effects can be intolerable to some individuals, it can be managed via dose adjustment or drug discontinuation. Other serious adverse events during use of colchicine, including liver and muscle toxicity, haemtological changes, neuropathy and death are very rare in clinical trials