Scandinavian Journal of Rheumatology

ISSN: 0300-9742 (Print) 1502-7732 (Online) Journal homepage: http://www.tandfonline.com/loi/irhe20

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To cite this article: G McCluskey, E O'Kane, D Hann, J Weekes & M Rooney (2012) Hypermobility and musculoskeletal pain in children: a systematic review, Scandinavian Journal of Rheumatology, 41:5, 329-338, DOI: 10.3109/03009742.2012.676064

To link to this article: http://dx.doi.org/10.3109/03009742.2012.676064

Published online: 28 May 2012.

REVIEW

Hypermobility and musculoskeletal pain in children: a systematic review

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Objective: To examine the evidence of an association between hypermobility and musculoskeletal pain in children.
Methods: A systematic review of the literature was performed using the databases PubMed, EMBASE, NHS Evidence, and Medline. Inclusion criteria were observational studies investigating hypermobility and musculoskeletal pain in children. Exclusion criteria were studies conducted on specialist groups (i.e. dancers) or hospital referrals. Pooled odds ratios (ORs) were calculated using random effects models and heterogeneity was tested using χ^2-tests. Study quality was assessed using the Newcastle–Ottawa Scale for case–control studies.
Results: Of the 80 studies identified, 15 met the inclusion criteria and were included in the review. Of these, 13 were included in the statistical analyses. Analysing the data showed that the heterogeneity was too high to allow for interpretation of the meta-analysis ($I^2 = 72\%$). Heterogeneity was much lower when the studies were divided into European ($I^2 = 8\%$) and Afro-Asian subgroups ($I^2 = 65\%$). Sensitivity analysis based on data from studies reporting from European and Afro-Asian regions showed no association in the European studies [OR 1.00, 95% confidence interval (CI) 0.79–1.26] but a marked relationship between hypermobility and joint pain in the Afro-Asian group (OR 2.01, 95% CI 1.45–2.77). Meta-regression showed a highly significant difference between subgroups in both meta-analyses ($p < 0.001$).
Conclusion: There seems to be no association between hypermobility and joint pain in Europeans. There does seem to be an association in Afro-Asians; however, there was a high heterogeneity. It is unclear whether this is due to differences in ethnicity, nourishment, climate or study design.

Joint hypermobility syndrome is a common cause of reported pain in rheumatology clinics in the UK, accounting for up to one-third of all pain complaints (1), and the prevalence of hypermobility has been reported to be as high as 58.7% in children (2). Nevertheless, there is still disagreement among clinicians regarding the importance of this condition.

The most commonly used diagnostic tool in clinical and epidemiological studies to detect hypermobility is the Beighton scoring system (3). This has been described as a useful initial screen but many clinicians consider that it cannot be relied upon to identify hypermobility (4–6). The Beighton system fails to take into account the degree of joint laxity and the possibility that hypermobility may only be present in one joint. A further problem is that it does not take into account other joints that may be hypermobile such as the shoulder, foot, and ankle joints. This was addressed in the revised 1998 Brighton criteria for the diagnosis of hypermobility, when it was recognized that a hypermobile patient may score as low as one provided other criteria are met (5, 7).

Factors such as age, ethnicity and sex have a remarkable effect on the prevalence of hypermobility in the population (4, 8). It is known that hypermobility varies with age and this poses a very important clinical question concerning the cut-off point for defining different age groups as hypermobile. Many studies have shown that hypermobility decreases with age, particularly in males (9–11). The trend is less clear in females, with some studies showing that the prevalence of hypermobility increases in females until early adolescence (12). Hypermobility also varies with gender; it is much more common in females than males (4, 13). There is also wide racial variation in hypermobility, with Asian and African races more hypermobile than those of Caucasian descent. Many studies have shown that there are very significant differences in the prevalence of hypermobility due to ethnicity (11, 14–16). It has been proposed that joint symptoms may be more prevalent in the 5–10% most mobile people in any given population, although the Beighton score that signifies this percentage will vary depending on the characteristics of the population being studied (3, 12). Defining

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Accepted 12 March 2012

DOI: 10.3109/03009742.2012.676064

hypermobility as the most mobile 5–10% of any given population might correct for the varying prevalence of hypermobility and thus make studies conducted on different ethnicities more comparable.

Some clinicians consider that hypermobility may in fact be beneficial rather than detrimental to the individual. For example it has been found that hypermobility among ballet dancers leads to a significantly decreased chance of injury (17), although other studies in ballet dancers have reported an increased chance of injury (18). Injury to wrist joints seems to be lower in hypermobile violinists and pianists of all ages (19).

In the current study we carried out a systematic review of the literature on observational studies investigating an association between hypermobility and musculoskeletal pain in children.

Methodology

In this review we aimed to determine whether hypermobility is associated with musculoskeletal pain in children and to explore the reasons for any association. We further aimed was to establish whether the top 5–10% most mobile of children experience more pain and whether any association with musculoskeletal pain is dependent on geographical location and ethnicity.

The review was conducted in accordance with the guidelines for carrying out a meta-analysis of observational studies (MOOSE) (20). The inclusion criteria were observational studies, reported in any language, that had investigated an association between hypermobility and musculoskeletal pain in children aged 0–19 years. We excluded studies that included specialist groups (e.g. dancers, athletes) and hospital referrals.

Four different investigators searched the literature. The databases searched were PubMed (1960–2010), EMBASE (1980–2010), NHS Evidence (1960–2010), and Medline (1966–2010). Keywords used in the searches were 'joint', 'hypermobility', 'pain', 'children', 'laxity', 'arthritis', and 'arthralgia' and these were used in various combinations. The search terms were deliberately broad to avoid the loss of relevant papers. In addition, the reference list of each of the articles was searched for further relevant publications.

A two-step process was used in the search for relevant studies. First, the titles and abstracts were analysed and rejected if they did not meet the inclusion criteria. Second, the full text of the articles was obtained and, if necessary, translated from the original language.

To conduct further analyses on the articles, attempts were made to contact the authors to obtain the raw data from the study, first by e-mail and then by letter. Attempts were also made to contact authors of studies that reported hypermobility but not musculoskeletal symptoms in case these data were collected despite not being included in the publication.

The studies were searched for data about the number of patients, proportion of patients who were hypermobile, and the prevalence of pain in the hypermobile and non-hypermobile group.

Qualitative assessment

The studies were assessed for quality using the Newcastle–Ottawa scale for case–control studies. They were scored according to three elements: participant selection, participant comparability, and exposure status. There were four questions on selection regarding: adequate definition for hypermobility, representativeness of the cases, selection of controls, and definition of controls. There was one question on comparability, involving comparability of cases and controls on the basis of the design or analysis. Finally, there were three questions on exposure regarding: ascertainment of pain, same method of ascertainment for cases and controls, and the non-response rate. Four marks were available for selection, 2 for comparability, and 3 for exposure, so that the total possible score was 9. GMcC and MR scored the papers independently using the Newcastle–Ottawa scale and a consensus was reached after discussion.

Statistical analysis

Our exposure variable was hypermobility and the outcome variable was pain. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) based on data extracted from each of the included studies. When data were amenable, these were pooled in forest plots and when heterogeneity (I^2) was > 30% we used a random effects model.

We also planned to perform sensitivity analyses to determine whether the results of the systematic review changed due to variation arising from different assumptions about the data and how they were used. Two were planned a priori. The first of these explored the effect of geographical location/ethnicity-based variation of hypermobility and compared estimates from European and Afro-Asian studies. A second sensitivity analysis compared pain levels in the 5–10% most mobile children in each study to explore whether an association with joint pain was more apparent in the cases of extreme mobility. Authors were contacted to provide the original data of their study to facilitate identifying the 5–10% most mobile children. This sensitivity analysis included nine studies that provided sufficient information on specific hypermobility scores and pain to reanalyse the original data. Sensitivity analyses were conducted using STATA. Forest plots were constructed using Review Manager 5 (RevMan 5).

Publication bias

We used three methods to identify publication bias in this area. We created a funnel plot in RevMan 5. Subsequently we tested for publication bias using Begg's and Egger's tests.

Results

The search strategy identified 80 articles (including five foreign-language articles in Hungarian, Slovak, Polish,

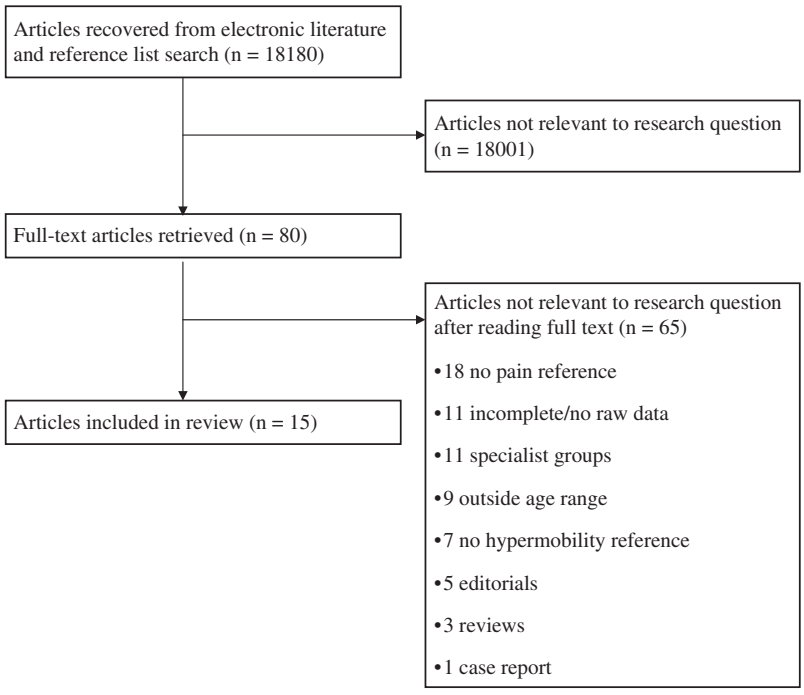

Figure 1. Search strategy used to identify studies for the review and meta-analysis with reasons for the exclusion of studies.

Finnish, and Spanish) that met the inclusion and exclusion criteria. After reviewing the articles in depth, this number was reduced to 15. Reason for exclusion of studies can be seen in Figure 1. Of the 15 studies included we were able to contact 11 authors and patient data were available in nine studies for further analyses.

Fifteen studies met the inclusion and exclusion criteria for the review. Of these, 11 were cross-sectional, two were longitudinal, and two were case–control studies. After contacting the authors it was revealed that both of the longitudinal studies followed up the samples from two of the cross-sectional studies included in the review (21, 22). We therefore excluded the data from both of these longitudinal studies so that the data from the same sample would not be used in the statistical analyses twice. This left 13 studies for the statistical analysis.

There was a wide variation in the prevalence of hypermobility in the studies, ranging from 7.8% to 58.7%. Most studies reported a prevalence of hypermobility from 20% to 40%. There was also a wide variation in the age of the subjects, ranging from 3 to 19 years. Most studies sampled children from a range of ages, with two studies only selecting children of a specific age: Qvindesland and Jonsson and Juul-Kristensen et al selected children aged 12 and 8 years, respectively. All studies had a comparable number of male and female subjects. The characteristics of the studies are presented in Table 1.

Qualitative assessment

The scores for each of the studies are shown in Table 2. Overall, the scores of the studies ranged from 5 to 9 (maximum score 9). All studies scored well on selection and comparability, with only three out of 12 studies failing to achieve 6 out of 6 in these sections, and those three scoring 5. Most studies scored poorly for the ascertainment of pain and loss to follow-up. Only three studies held a structured interview with the subjects to determine whether or not pain was present and many did not give data on the loss to follow-up. The studies all varied on how they measured pain and did not give sufficient detail on how pain was classified and on whether the subjects knew that they had hypermobility when reporting pain.

Meta-analyses

The OR of musculoskeletal pain for hypermobile children compared to non-hypermobile children for all studies was 1.52 (95% CI 1.14–2.03). The forest plot is shown in Figure 2. However, there was marked heterogeneity ($I^2 = 72\%$).

The studies were divided into subgroups for the reasons outlined earlier. There were seven studies in the European group and six in the Afro-Asian group. in the European group we included six European studies (two from Italy and one from each of Iceland, Denmark, Holland, and Finland) and one American study. It was probable that the sample in the American study was of European descent but it was not possible to determine their ethnicity. Analyses were conducted on this subgroup both including and excluding the American study and little difference was found in the results. The Afro-Asian group contained two Indian, two Turkish, one Egyptian, and one Israeli study. The Turkish studies were from eastern Turkey and so were classified as Asian rather than European.

Table 1. Characteristics from each of the studies used in the systematic review including information on the subjects, location, and criteria for defining both hypermobility and musculoskeletal pain.

Study (year of publication)	Journal	Participant details	Location	Hypermobility measurement	Hypermobility prevalence (%)	Pain measurement	Person questioned about pain
Arroyo et al (1998)	J Rheumatol	Subjects: School children n = 192 M/F: 83/109 Age: 5–19	Texas (USA)	Beighton scale (5/9)	66/192 (34.4)	Questionnaire with 12 questions on pain, authors only presented pain yes/no	Parent
El-Garf et al (1998)	J Rheumatol	Subjects: School children n = 997 M/F: 499/498 Age: 6–15	Egypt	Beighton scale (4/9)	161/997 (16.1)	Interview with MSK history. Presence of arthralgia was used to determine pain yes/no	Child
Gedalia and Press (1991)	J Pediatr	Subjects: School children n = 429 M/F: 226/203 Age: 6–14	Beer-Sheva (Israel)	Carter and Wilkinson criteria (3/5)	53/429 (12.4)	Monthly questionnaire for 1 year with seven questions on pain. Recurrent arthralgia ($\geq$ 2 episodes in the year) was used to classify pain yes/no	Child
Hasija et al (2008)	Clini Exp Rheumatol	Subjects: School children n = 829 M/F: 436/393 Age: 3–19	Mumbai (India)	Beighton scale (4/9)	487/829 (58.7)	Questionnaire for detailed MSK history. Not stated what was used for analysis	Parent
Juul-Kristensen et al (2009)	Pediatrics	Subjects: School children n = 349 Male/Female: 189/160 Age: 8	Denmark	Beighton scale (5/9)	64/349 (18.3)	75 questions on health. Arthralgia in $\geq$ 4 joints for > 3 months was used to determine pain yes/no	Child and parent together
Leone et al (2009)	Arch Dis Child	Subjects: School children n = 1230 M/F: 516/530 Age: 7–15	Italy	Beighton scale (4/9)	370/1046 (35.4)	Questionnaire on MSK pain over the past 3 months (never, seldom, once monthly, once weekly, more, every day). The pain group was defined as pain $\geq$ 1 weekly	Child
Mikkelsson et al (1996)	J Rheumatol	Subjects: School children n = 1637 M/F: 802/835 Age: 9–12	Finland	Beighton scale (6/9)	127/1637 (7.8)	Questionnaire on MSK pain over the past 3 months (never, seldom, once monthly, once weekly, more, every day). The pain group was defined as pain $\geq$ 1 weekly	Child

Table 1. (*Continued*)

Study (year of publication)	Journal	Participant details	Location	Hypermobility measurement	Hypermobility prevalence (%)	Pain measurement	Person questioned about pain
Qvindesland and Jonsson (1999)	Rheumatology	Subjects: School children n = 267 Male/Female: 124/143 Age: 12	Iceland	Beighton scale (4/9)	74/267 (27.7)	Questionnaire. Not stated what was used to decide presence of pain	School nurse
Ruperto et al (2004)	Cli Exp Rheumatol	Subjects: School children n = 311 M/F: NS Age: 6.3–19.3	Italy	Beighton scale (5/9)	106/311 (34.1)	Data on pain were recorded using VAS but not reported in article. We analysed these data after requesting them and used a score ≥ 2 to define pain	Child
Seckin et al (2005)	Rheumatol Int	Subjects: School children n = 861 M/F: 428/433 Age: 13–19	Ankara (Turkey)	Beighton scale (4/9)	101/861 (11.7)	Interview with MSK history. Arthralgia was used to determine pain yes/no	Child
Smits-Engelsman et al (2011)	J Pediatr	Subjects: School children n = 551 M/F: 258/293 Age: 6–12 years	Holland	Beighton scale (7/9)	50/551 (9.1)	Information on child's background health was recorded. However, no information is given on questions asked or what was used to define pain	N/S
Viswanathan and Khubchandani (2008)	Clini Exp Rheumatol	Subjects: School children n = 433 M/F: NS Age: 3–9	Mumbai (India)	Beighton scale (5/9)	177/433 (40.9)	Interview to investigate presence of growing pains using Peterson's criteria. Presence of growing pains was used to determine pain yes/no	Child
Yazgan et al (2008)	Rheumatol Int	Subjects: School children n = 934 M/F: 509/413 Age: 5–10	Sanliurfa (Turkey)	Beighton scale (4/9)	363/922 (39.4)	Interview to collect data on previous 6 months' history of MSK pain. Presence of arthralgia was used to determine pain yes/no	Child

M, Male; F, female; MSK, musculoskeletal; VAS, visual analogue scale; NS, not significant.

Table 2. The qualitative scoring system that was used to assess the studies. The maximum scores available were: 4 for selection, 2 for comparability, and 3 for outcome.

Study (year)	Selection	Comparability	Outcome	Total
Arroyo et al (1988)	3	2	0	5
El-Garf et al (1998)	4	2	2	8
Gedalia and Press (1991)	3	2	1	6
Hasija et al (2008)	4	2	1	7
Juul-Kristensen et al (2009)	4	2	2	8
Leone et al (2009)	4	2	2	8
Mikkelsson et al (1996)	4	2	2	8
Qvindesland and Jonsson (1999)	4	2	1	7
Ruperto et al (2004)	4	2	2	8
Seckin et al (2005)	3	2	1	6
Smits-Engelsman et al (2011)	4	2	1	7
Viswanathan and Khubchandani (2008)	4	2	3	9
Yazgan et al (2008)	4	2	3	9

The sensitivity analysis based on the European subgroup was not statistically significant (OR 1.00, 95% CI 0.79–1.26) while the Afro-Asian subgroup (OR 2.01, 95% CI 1.45–2.77) was statistically significant. Meta-regression showed that there was a highly significant difference in the pain scores and hypermobility between the two subgroups ($p < 0.001$). The heterogeneity was also lower, with the I^2 value for the European and Afro-Asian studies being 8% and 65%, respectively.

Sufficient data were available for nine of the 13 studies to undertake a second meta-analysis to determine whether there was a greater association in the most mobile 5–10% of children. Six of the studies were from the European group and three from the Afro-Asian group. The forest plot for this can be seen in Figure 3. Overall, the OR of musculoskeletal pain with hypermobility was lower than the first meta-analysis of the 13 studies and it was not statistically significant (OR 1.29, 95% CI 0.84–2.00). The

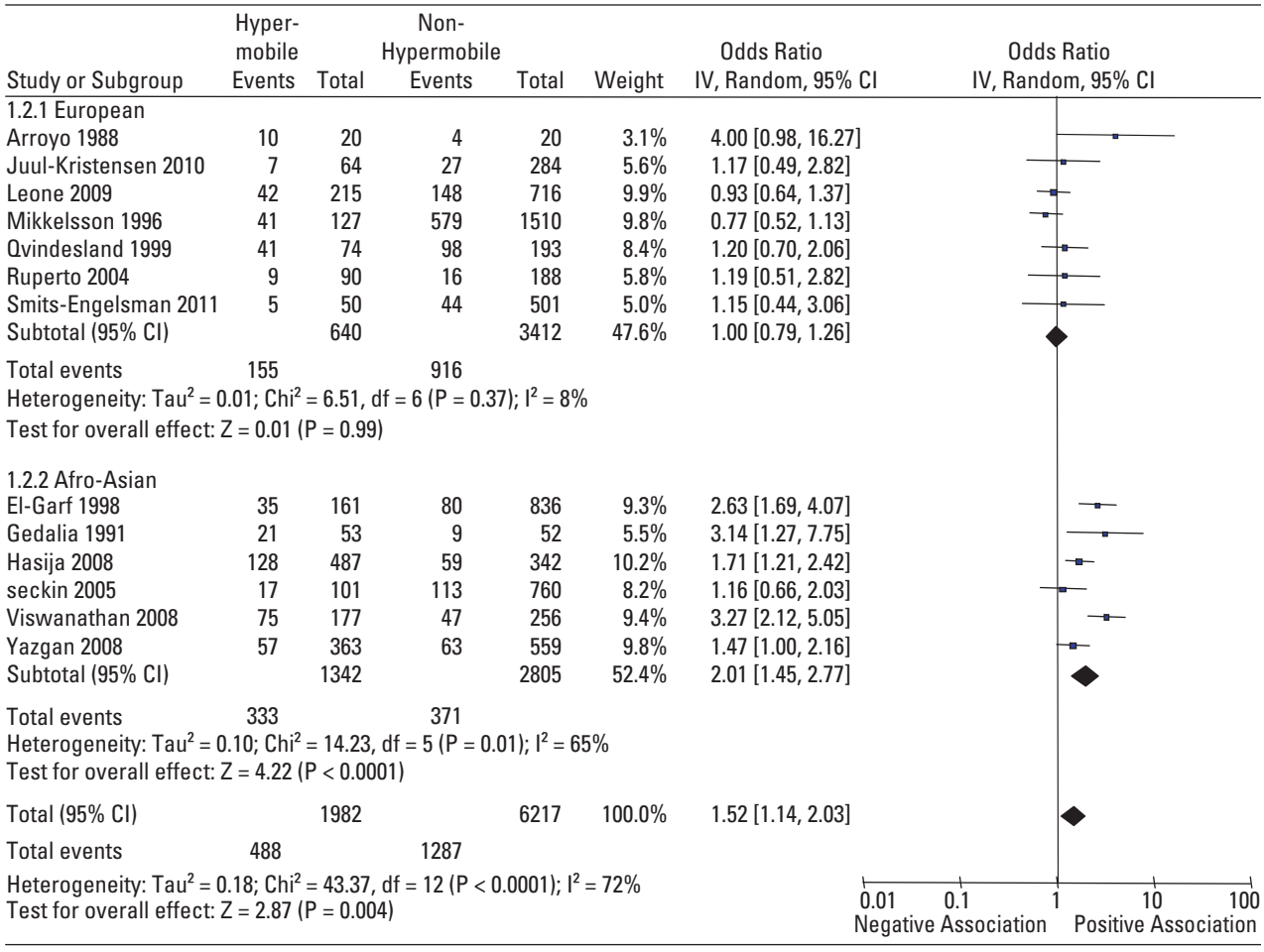

Figure 2. Forest plot showing all 13 studies divided into the European and Afro-Asian subgroups.

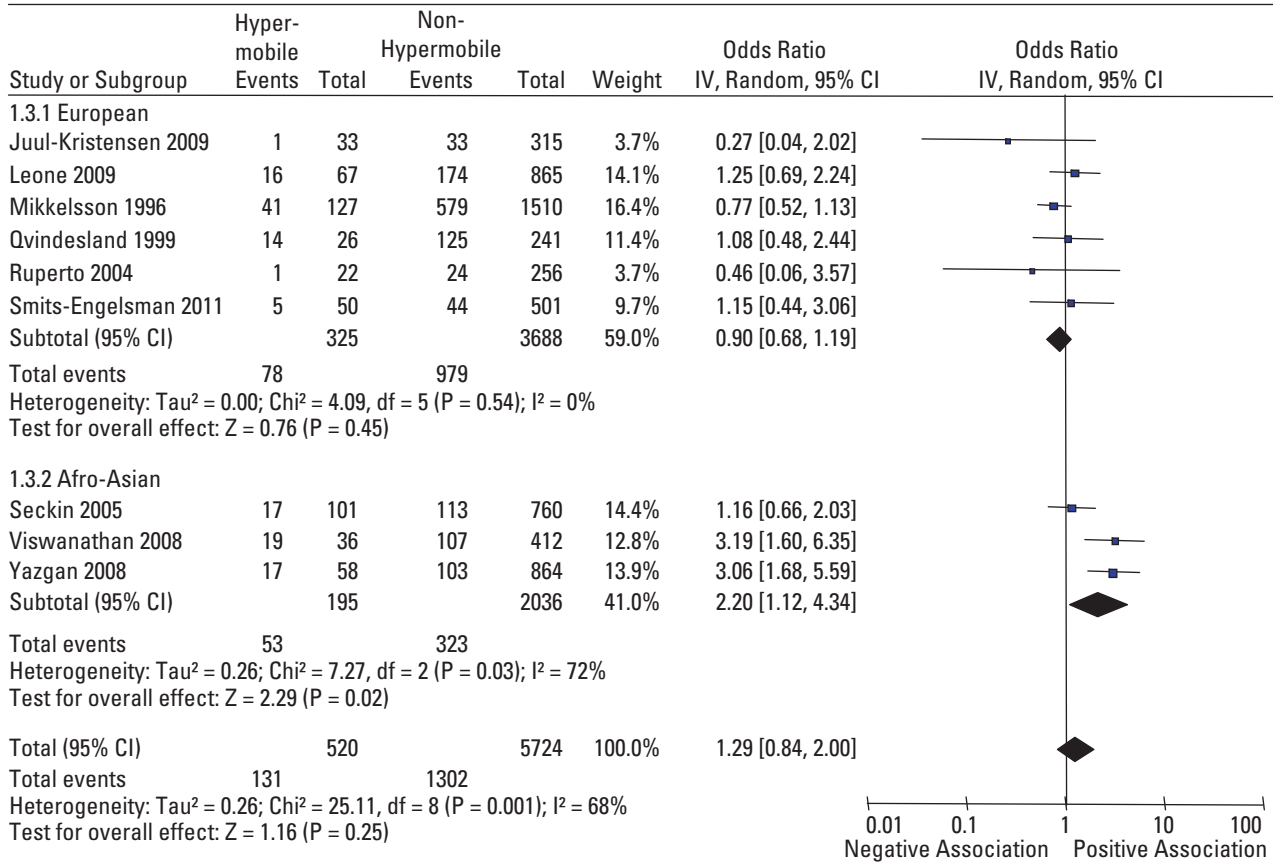

Figure 3. Forest plot showing the meta-analysis of nine studies, examining the most mobile 5–10% of each study sample.

OR was also lower in the European subgroup (OR 0.90, 95% CI 0.68–1.19), although it was slightly higher in the Afro-Asian subgroup (OR 2.20, 95% CI 1.12–4.34).

The meta-regression demonstrated that there was still a statistically significant difference between the subgroups ($p < 0.001$). The heterogeneity was still high for the nine studies ($I^2 = 68\%$). However, for the six studies in the European subgroup the heterogeneity was extremely low ($I^2 = 0\%$), while for the three studies in the Afro-Asian subgroup the heterogeneity remained high ($I^2 = 72\%$).

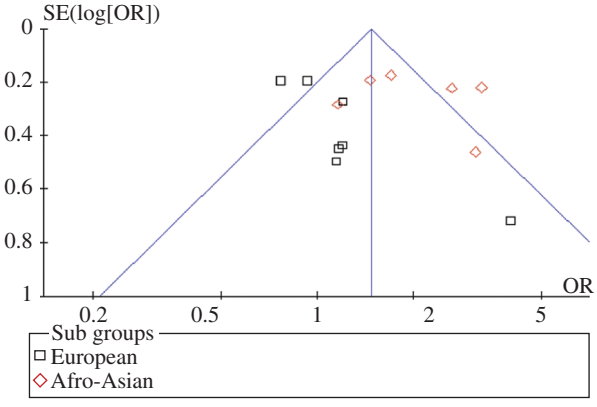

Figure 4. Funnel plot to determine publication bias.

Publication bias

We used three methods to identify publication bias in this area. First, we created a funnel plot in RevMan 5 (Figure 4). Then we tested for publication bias using Begg's and Egger's tests. From the funnel plot, there was some evidence of asymmetry but both Begg's and Egger's tests did not reveal evidence of publication bias ($p = 0.37$ and $p = 0.36$, respectively).

Discussion

Joint hypermobility has long been linked with musculoskeletal complaints. However, the studies carried out to investigate this association have found conflicting evidence of an effect. The purpose of this observational systematic review was to determine whether joint hypermobility is associated with musculoskeletal pain in children.

The meta-analysis on all 13 of the studies included demonstrated a slight but statistically significant association between hypermobility and musculoskeletal pain (OR = 1.52, 95% CI 1.14–2.03). However, there was a high heterogeneity in this result ($I^2 = 72\%$). This means that there were significant differences in the way that each of the studies used in the meta-analysis was carried out, and therefore the results from this meta-analysis should be interpreted with great caution.

There are many possible reasons for this very high variation. Numerous articles have reported differences in hypermobility score depending on (i) gender, with girls being more likely to be hypermobile (5, 13, 15, 21, 23–27), (ii) age, with younger people tending to be more hypermobile (5, 10, 13, 28), and (iii) ethnicity/geographical location, with those in warmer climates tending to be more hypermobile as well as those of Asian or African descent (29). It has been suggested that the observed differences in gender may be due to hormones produced by females and although hypermobility is more prevalent in females, symptomatic cases are more likely to be found in males (30).

There was wide variation in the prevalence of hypermobility in the 13 studies: from 7.8% (33) to 58.7% (28). A recent UK study with more than 6000 14-year-old children found the prevalence of hypermobility to be 19.2% (27). Studies have reported that joint mobility is normally distributed and hypermobility should only be considered as mobility in excess of 2 standard deviations away from the mean range of joint mobility. The Beighton score that determines hypermobility should therefore only identify the top 5–10% most mobile children (12, 31). If a sample study is showing hypermobility in 58.7% of the subjects (28), then this cannot be referred to as hypermobility, because having hypermobility is in fact more common in this population than having a 'normal' range of mobility (8).

The studies were all comparable in the ratio of males to females but a large range of age groups was used. Of the studies reporting a high prevalence of hypermobility, most involved younger children, aged < 10 years, while most studies reporting a low prevalence of hypermobility were on older children. Another factor that could lead to a variation in the prevalence is the criteria that were used to determine hypermobility. Beighton scores for prevalence were reported in the range 4 to 7: obviously, studies that chose a Beighton score of 7 recorded a lower prevalence than those that chose a score of 4.

To attempt to reduce the effect of the prevalence of hypermobility on the results, we contacted the authors to obtain their original data so that we could use a cut-off for hypermobility that would identify the most mobile 5–10% of each study population. If hypermobility is associated with joint pain, it would be expected that the association would be most evident when examining the most mobile 5–10% children of each study (8). Interestingly, our results found that the OR of pain was in fact lower in the top 5–10% most mobile children (OR 1.29, 95% CI 0.84–2.00) compared to our original analysis (OR 1.52, 95% CI 1.14–2.03). This suggests that the association is not stronger in the most mobile children. Indeed, the European subgroup had an OR of 0.90 (95% CI 0.68–1.19, $I^2 = 0\%$).

To reduce the effect of varying degrees of mobility due to ethnicity, the studies were subdivided into a European group, where a lower prevalence of hypermobility would be expected, and an Afro-Asian group, where a higher prevalence of hypermobility would be expected. In this way we were able to compare the two groups to see whether dividing the groups by ethnicity would reduce the heterogeneity, but to also see whether the association may be more clinically relevant depending on ethnicity. The result of the meta-analysis on the subgroups showed an OR of 1.00 (95% CI 0.79–1.26) in the European subgroup and an OR of 2.01 (95% CI 1.45–2.77) in the Afro-Asian group. We believe we were justified in dividing the studies into two groups based on geographical location of the study and ethnicity of the participants because these are recognized determinants of the prevalence of hypermobility. This decision is substantiated by the meta-regression analysis, which demonstrated a highly statistically significant difference between the two subgroups, suggesting that there is a fundamental difference between the subgroups. Of note, in the second sensitivity analysis, the OR of the European group was lower (OR 0.90, 95% CI 0.68–1.19) and the OR of the Afro-Asian group was greater (OR 2.20, 95% CI 1.12–4.34) than in the first meta-analysis.

These results suggest that hypermobility is not clinically important for the children from the European regions. However, there does seem to be an association with joint pain and those of Asian or African descent. The explanation for this is unclear but may be related to ethnicity, nutrition, climate, or study design.

This systematic review only examined the association between hypermobility and musculoskeletal pain, and it is important to understand that many other factors have an influence over whether an individual will suffer from pain. It has been shown that there are important factors that influence the severity of pain, including physical fitness, muscle strength, and psychological coping mechanisms.

Limitations of the review

There was a high heterogeneity for the overall results in each meta-analysis: $I^2 = 72\%$ and 68% in the first and second meta-analysis, respectively. Therefore, it may not be appropriate to meta-analyse these data, and these results should be interpreted with caution. However, the heterogeneity of the two subgroups was much lower: 8% and 65% in the European and Afro-Asian subgroups, respectively, in the first meta-analysis; and 0% and 72% in the European and Afro-Asian subgroups respectively in the second meta-analysis. Therefore, there is a statistically significant difference in data from the different continents.

A further explanation for the high degree of heterogeneity may lie in the variety of pain measurement tools used in the studies. Although it would have been ideal to undertake a sensitivity analysis on pain, the marked variation on how pain was measured made this impossible. The way these tools were used and pain recorded could result in considerable bias. Most studies used a questionnaire to be filled in by either the child or the parent, and in one case by the school nurse. In five studies it was not clear whether the questionnaire was given before or after the measurement of hypermobility and also whether the child or parent knew

they were hypermobile prior to completing it (2, 32–36). Only four studies had a structured interview with the children to determine whether the child had joint pain (23, 37, 38). Seven studies provided the children with questionnaires (26, 33–36, 39, 40) and two studies made no mention of how pain was measured (2, 41).

The studies differed not only on how they measured joint pain but also on how they classified it. Some studies classified a child as having musculoskeletal pain if they had a small amount of pain once a week, with no mention of its frequency or duration. Other studies measured chronic pain, with the child needing to have had more than 3 months of pain every day in one or more joint.

Although we were only able to examine studies investigating hypermobility and joint pain, it has been suggested that hypomobility may also be associated with joint pain. It is possible that not only the most mobile but also the least mobile children in a population will develop joint pain. In a study using a hyperextensiometer to measure joint mobility, it was found that patellar pain was present in both extreme ranges of mobility (6). Another study has shown that children with hypermobility and those with hypomobility suffered from increased amounts of pain when compared to controls (42).

Our findings suggest that there is no association between joint pain and hypermobility in children from Europe and America. However, there is ongoing uncertainty for children from other regions and ethnicities. The findings of this systematic review highlight the need for high-quality studies using validated tools and consistent data collection.

Directions for further research

Any further research into the association between joint hypermobility in the African and Asian subcontinent should include nutritional data as well as the use of validated musculoskeletal pain questionnaires.

Conclusion

Because of the high heterogeneity observed it is not possible to draw a conclusion from the meta-analysis of all the studies examined. However, we found no association between joint pain and hypermobility in children from the European and American regions, with low heterogeneity. There does seem to be an association in the Afro-Asian subcontinents. Whether this is directly related to hypermobility or other confounders such as nutritional status remains unclear. However, again because the relatively high heterogeneity this finding should be considered with caution.

Acknowledgements

We thank the following researchers and their teams for answering our queries and for providing us with the raw data from their studies to enable us to perform further analyses: Dr A Gedalia, Dr A El-Metwally, Dr B Juul-Kristensen, Dr A Ravelli, Professor J Cheng, Dr R Khubchandani, Dr R Hasija, Dr V Viswanathan, Dr V Leone, Dr P Yazgan, Dr H Jonsson, and Professor N. Lamari. We also thank Dr C Cardwell for help with the data analysis and Dr F Crawford for help and advice on this study.

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