Prognostic factors for recurrent idiopathic clubfoot deformity: a systematic literature review and meta-analysis

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Submitted 2021-03-04. Accepted 2021-08-09.

Background and purpose — After initial clubfoot correction through Ponseti treatment, recurrence rates range from 26% to 48%. Even though various factors have been associated with increased recurrence risk, systematic assessments of the prognostic capacity of recurrence risk factors and their clinical relevance are lacking. Therefore we assessed clinically relevant prognostic factors for recurrent idiopathic clubfoot deformity after initial correction through Ponseti treatment.

Methods — PubMed, Embase, Cinahl, and Web of Science were systematically searched for studies investigating the association between clinically relevant factors and recurrence rates. Prognostic factors were qualitatively assessed and included in the meta-analysis if ≥ 2 studies investigated the same factor and methods were comparable.

Results — 34 articles were included in the qualitative synthesis, of which 22 were also included in the meta-analysis. Meta-analysis revealed that poor evertor muscle activity (OR = 255, 95% CI 30–2,190), brace non-compliance (OR = 10, CI 5–21), no additional stretching (OR = 31, CI 10–101), more casts (OR = 3.5, CI 1.6–7.8), lower education level of parents (OR = 1.8, CI 1.2–2.6), non-marital status of parents (OR = 1.8, CI 1.1–3.0), and higher Dimeglio scores (OR = 1.9, CI 1.2–3.3) were associated with higher recurrence rates.

Interpretation — Brace non-compliance and poor evertor muscle activity have been identified as main recurrence risk factors and are therefore important to be closely monitored during clinical follow-up of clubfoot patients. Adding additional stretching during the bracing protocol might be promising in the quest to prevent relapse, but scientific evidence for clear clinical treatment recommendations is still limited.

Idiopathic clubfoot is typically treated according to the Ponseti method involving repetitive manipulation and casting, in most cases an Achilles tenotomy and a foot abduction brace until the age of 4. The goal of the extensive bracing regime is to prevent recurrence by opposing the deforming forces at the medial ankle–foot joints that persist or reoccur after initial correction of the clubfoot (Ponseti 2002, Dobbs and Gurnett 2009, Hosseinzadeh et al. 2017). However, between 26% and 48% of the children treated with the Ponseti method experience a clubfoot recurrence (Hosseinzadeh et al. 2017). A major challenge of current clubfoot research is to categorize children based on recurrence risk and identify those children in need of preventive interventions to reduce recurrence risk.

Although the exact underlying pathomechanism of clubfoot recurrence remains to be established, it is assumed that recurrences are caused by the same pathology as the initial deformity (Ponseti 2002). After initial correction, persisting or reoccurring retracting fibrosis in the tarsal ligaments and their surrounding structures pulls on the medial ankle and foot joints. In some children these deforming forces cannot be sufficiently opposed by the evertor muscles (e.g., peroneus longus and brevis), since these remain weak (Ponseti 2002, Chu and Lehman 2012, Gelfer et al. 2014). This imbalance between in- and everting ankle–foot joint forces might gradually increase and lead to clubfoot recurrence. In line with this pathomechanism is the finding that children strictly adhering to the bracing regimen are less likely to experience a recurrence as compared with children who have poor brace compliance (Dobbs et al. 2004, Avilucea et al. 2009). Similarly, those children with a better ability to oppose the deforming medial ankle–foot joint forces with activity of their evertor muscles seem to have a lower recurrence risk (Gelfer et al. 2014, Little et al. 2019). Other factors that have previously

DOI 10.1080/17453674.2021.1982576

been associated with the risk of clubfoot recurrence are accessibility to treatment resources, frequency and number of cast changes, or the severity of the initial deformity (Dobbs et al. 2004, Avilucea et al. 2009, Zhao et al. 2014, Goldstein et al. 2015). The main limitation in current literature is the lack of a systematic overview of relevant recurrence risk factors and their prognostic capacity.

This literature review and meta-analysis provides a systematic overview of factors associated with the risk of recurrence after initial correction with the Ponseti method and quantifies the strength of each recurrence risk factor and its clinical relevance. Based on the proposed pathomechanism of force imbalances in recurrent clubfoot deformity (Ponseti 2002), we hypothesize that brace compliance and evertor muscle function have the strongest prognostic capacity for clubfoot recurrence.

Methods

The systematic literature search and meta-analysis were conducted in accordance with the PRISMA guidelines and registered with PROSPERO (CRD42020172434).

Literature search

Studies published up to March 5, 2020 were systematically searched in 4 databases (PubMed, Embase, Cinahl, and Web of Science). A search string (Appendix 1, see Supplementary data) was formulated for each database using database-specific MeSH terms, title, abstract and text search words, wildcards (*) and Boolean operators (AND and OR). The following terms and their synonyms were used: clubfeet, Ponseti, and recurrence.

Eligibility criteria and study selection

Studies were included if (i) written in English, Dutch, or German, (ii) patients were diagnosed with idiopathic clubfoot deformity and (iii) treated according the Ponseti method, (iv) included the occurrence of recurrent clubfeet deformity, (v) provided statistical assessments of an association between clubfoot recurrence and prognostic factor(s) in terms of odds ratio or other risk estimates such as hazard ratios. Exclusion criteria were (i) < 5 participants, (ii) study was not primary research, (iii) study considered non-idiopathic, secondary recurrence, and/or neglected clubfeet. Neglected clubfeet were defined as: no treatment given before the age the child starts walking (12 months) (Sutherland et al. 1980, Adegbehingbe et al. 2017).

The selection process started by removing duplicates, followed by screening of titles and eventually abstracts and full texts of the respective studies. 2 reviewers (HS and CG) independently assessed the eligibility criteria. If at least 1 reviewer included a title, it was included in the abstract phase. Abstracts and full texts were included if agreement existed between the 2 assessors. Disagreements were solved in a discussion meeting. Reference lists of included articles were checked in additional relevant studies.

Data extraction

Data extraction was performed by HS. In the case of unreported data authors were contacted via email. Data extraction was performed on study characteristics, participant characteristics, treatment details, and the main outcome measures.

Risk of bias assessment

The risk of bias for the individual papers was assessed by 2 independent researchers using the prognostic form of the Cochrane Collaboration's risk of bias tool (Appendix 2, see Supplementary data) . Every item was scored with "low risk" (+), "high risk" (–), or "unclear" (?) (Scholten et al. 2013). The forms were compared and discussed for final conclusion. Measurements of prognostic factors were marked as high bias if one of the measurements was done in a self-reporting way. The overall risk of bias was judged to be low if all domains were marked low, moderate if > 2 domains were marked unclear and others low, serious if one domain was judged high risk, critical if multiple domains were marked high risk, and unknown if information on most domains was lacking (Sterne et al. 2016).

Data synthesis and statistical analyses

Qualitative and quantitative data synthesis was performed on all factors found in the included studies. A meta-analysis was performed using Review Manager (RevMan version 5.3) (Cochrane Collaboration 2014) when ≥ 2 studies investigate the same prognostic factor and methods for assessment were comparable. Absolute values of the number of participants were used to perform meta-analyses (Mantel–Haenzel) and determine the recurrence risk in terms of odds ratio (OR) with an 95% confidence interval (CI). Fixed effect was used if heterogeneity was low (I^2 < 50%), and random effect if heterogeneity was high (I^2 > 50%). To improve clinical interpretation of the findings from the random effect meta-analysis, prediction intervals were computed when > 10 studies were included in the meta-analysis (Deeks et al. 2021). In addition, an odds ratio > 3 was marked as of clinical significance (Kraemer 1992, Higgins et al. 2021). To improve overall interpretability, significant findings were also presented as risk percentages using the following computation: risk percentage = odds/(1+odds)*100 (Higgins et al. 2021). A risk percentage of 10% would mean that 10 out of 100 children will have a recurrent pathology. Data from studies investigating the association between compliance and recurrence rates was transformed to allow pooling with studies investigating the association of non-compliance. Furthermore, reference groups were determined for categorical and continuous outcomes, based on the cut-off points that were presented in the majority of the studies (Appendix 2, see Supplementary data).

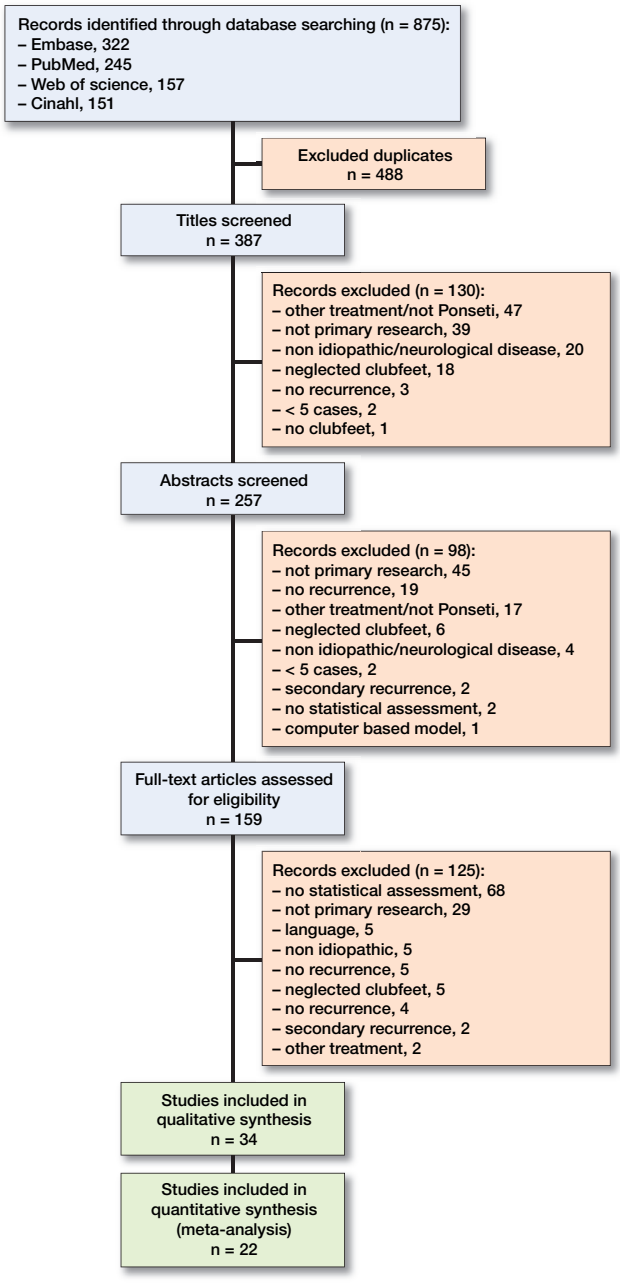

Figure 1. PRISMA flow diagram of results.

Funding and potential conflicts of interest

No funding was received to perform this study. The authors have no conflicts of interest to declare.

Results

Study selection and characteristics

875 articles were identified in the initial search. After study selection (Figure 1), 34 articles were included for qualitative synthesis and 22 for meta-analysis.

Table 1 (see Supplementary data) summarizes the study characteristics of the included articles. This review included 2,987 idiopathic clubfeet treated with the Ponseti method, of which 70% of the patients were male. Sample sizes ranged from 23 to 308 children and the average recurrence rate was 22% (5–49%). The initial age of manipulation by cast treatment was on average 50 days, and the average age at recurrence was 1.6 years. Follow-up period was reported in 31 articles, with an average of 3 years (13 months–8 years). The bracing protocol was documented in 29 studies. Bracing duration ranged between 2 and 5 years. Brace compliance was reported in 21 studies, with an average of 76% (0–100%).

Risk of bias

An overall judgment of the risk of bias assessment is given in Table 1. Although all studies described the prognostic factors clearly and a valid recruitment of participants was performed, all studies showed unclear or high risk of bias on 1 or more items of the checklist (Appendix 3, see Supplementary data).

Prognostic factors for clubfoot recurrence

Musculoskeletal factors

23 studies assessed the association of recurrence rates and 9 musculoskeletal factors (Table 2). 3 factors could be included in a meta-analysis.

2 studies investigated the association between manually tested evertor muscle activity and recurrence risk. Both were included in the meta-analysis. Poor evertor muscle activity was associated with 225 times higher odds of clubfoot recurrence (CI 30–2,190; 99.6% risk; Figure 2A, see Supplementary data) exceeding the threshold value for clinical significance. The assessment of initial Dimeglio score was reported in 11 studies, of which 6 could be included in the meta-analysis. A higher Dimeglio score was associated with 1.9 times higher odds of clubfoot recurrence (CI 1.2–3.3; 66% risk; Figure 2B, see Supplementary data). However, 4 of the 5 studies not included in the meta-analysis did not find an association. The meta-analysis on initial Pirani scores included 3 out of 8 studies, but did not reveal a significant association (Figure 2C, see Supplementary data). This was in line with the remaining 5 studies.

Lower overall joint laxity as measured with the Beighton score was associated with a 5.3 times higher odds of clubfoot recurrence in 1 study (CI 1.3–22). Other investigated musculoskeletal factors showed no clear association with recurrence rates.

Genetics

17 studies assessed the association between 3 genetic factors and recurrence rates (Table 3). 2 factors were included in a meta-analysis and no association was found for family history or gender (Figure 3, see Supplementary data). Based on qualitative synthesis, a significant association was found for

Table 2. Overview and outcome of studies: presented musculoskeletal factors for risk of recurrence

Musculoskeletal factor	Significant association	Not significant association
Decreased dorsiflexion		
Before tenotomy(radiographic)	(O'Halloran et al. 2015)	(Kang and Park 2015)
After tenotomy (goniometer)	(Hosseinzadeh et al. 2016)	
Decreased lateral tibio-calcaneal angle (radiographic)	(Kang and Park 2015)	(O'Halloran et al. 2015)
Lower joint laxity (Beighton score)	(Cosma et al. 2018)	
Poor evertor muscle activity	(Gelfer et al. 2014), (Little et al. 2019)	
Severity of clubfeet deformity		
Initial Dimeglio score	(Brazell et al. 2019), (Panjavi et al. 2012), (Sangiorgio et al. 2017)	(Clarke et al. 2011), (Hallaj-Moghaddam et al. 2015), (Jochymek and Peterkova 2019), (Kang and Park 2015), (Kuzma et al. 2019), (Limpaphayom and Sailohit 2019), (Ramírez et al. 2011), (Vo and Huynh 2016)
Initial Pirani score		(Avilucea et al. 2009), (Cosma et al. 2018), (Dinesh et al. 2017), (Gelfer et al. 2014), (Haft et al. 2007), (Jochymek and Peterkova 2019), (Shabtai et al. 2015), (Zhao et al. 2018)
Higher talar dysplasia		(Jochymek and Turek 2018)
Walking age	(Zionts et al. 2014)	(Hallaj-Moghaddam et al. 2015), (Shabtai et al. 2015)

Table 3. Overview and outcome of studies: presented genetic factors for risk of recurrence

Genetic factor	Significant association	Not significant association
Family history		(Haft et al. 2007), (Panjavi et al. 2012)
Race/ethnicity	(Avilucea et al. 2009)	(Chong et al. 2014), (Haft et al. 2007), (Kuzma et al. 2019), (Zhao et al. 2018)
Sex		(Avilucea et al. 2009), (Brazell et al. 2019), (Chong et al. 2014), (Clarke et al. 2011), (Cosma et al. 2018), (Hallaj-Moghaddam et al. 2015), (Kang and Park 2015), (Kuzma et al. 2019), (Limpaphayom and Sailohit 2019), (Little et al. 2019), (O'Halloran et al. 2015), (Panjavi et al. 2012), (Ramírez et al. 2011), (Sangiorgio et al. 2017), (Willis et al. 2009), (Zhao et al. 2018)

Table 4. Overview and outcome of studies: presented demographic factors for risk of recurrence

Demographic factor	Significant association	Not significant association
Family		
Age of parents		(Chong et al. 2014), (Hallaj-Moghaddam et al. 2015)
Economic status	(Mootha et al. 2011)	
Education level	(Avilucea et al. 2009)	(Cosma et al. 2018), (Kuzma et al. 2019), (Panjavi et al. 2012), (Ramírez et al. 2011), (Sangiorgio et al. 2017)
Employment		(Kuzma et al. 2019)
Income	(Avilucea et al. 2009)	(Chong et al. 2014), (Kuzma et al. 2019), (Ramírez et al. 2011), (Sangiorgio et al. 2017)
Insurance	(Avilucea et al. 2009)	(Ramírez et al. 2011), (Sangiorgio et al. 2017)
Marital status parents	(Avilucea et al. 2009)	(Kuzma et al. 2019), (Sangiorgio et al. 2017)
Laterality		(Brazell et al. 2019), (Chong et al. 2014), (Clarke et al. 2011), (Kang and Park 2015), (Limpaphayom and Sailohit 2019), (Panjavi et al. 2012), (Ramírez et al. 2011), (Sangiorgio et al. 2017), (Shabtai et al. 2015), (Zhao et al. 2018)

Native American ethnicity and recurrence rates in Avilucea et al. (2009); other studies showed no association with ethnicity.

Demographic factors

15 studies assessed the association between 8 demographic factors and recurrence rates (Table 4). 5 factors were assessed in a meta-analysis and showed significant associations between recurrence rates and a lower education level of parents (OR = 1.8, CI 1.2–2.6; 64% risk) and non-marital status of parents (OR = 1.8, CI 1.1–3.0; 64% risk; Figure 4A, D, see Supplementary data). No associations were found for income level, insurance or laterality (Figure 4B, C, E, see Supplemen-

Table 5. Overview and outcome of studies: presented treatment factors for risk of recurrence

Treatment factor	Significant association	Not significant association
Additional stretching	(Panjavi et al. 2012)	(Limpaphayom and Sailohit 2019)
Accelerated Ponseti treatment	(Morcuende et al. 2005)	
Brace duration	(Mahan et al. 2017)	
Casting		
Age of completion casting	(Kuzma et al. 2019)	
Duration casting	(Kuzma et al. 2019)	(Ramírez et al. 2011)
Number of casts	(Chong et al. 2014)	(Dinesh et al. 2017), (Gelfer et al. 2014), (Haft et al. 2007), (Hallaj-Moghaddam et al. 2015), (Kuzma et al. 2019), (Little et al. 2019), (Morcuende et al. 2004), (Morcuende et al. 2005), (Shabtai et al. 2015), (Zhao et al. 2018)
Initial age at start of treatment	(Willis et al. 2009)	(Chong et al. 2014), (Gelfer et al. 2014), (Haft et al. 2007), (Hallaj-Moghaddam et al. 2015), (Kang and Park 2015), (Kuzma et al. 2019), (Limpaphayom and Sailohit 2019), (Little et al. 2019), (Liu et al. 2018), (Ramírez et al. 2011), (Mootha et al. 2011), (Morcuende et al. 2004), (Morcuende et al. 2005), (O'Halloran et al. 2015), (Vo and Huynh 2016), (Zhao et al. 2018)
Longer follow-up time	(Chong et al. 2014)	(O'Halloran et al. 2015)
Previous treatment		(Cosma et al. 2018), (Mootha et al. 2011), (Morcuende et al. 2005), (Morcuende et al. 2004), (Ramírez et al. 2011), (Willis et al. 2009)
Surgeon vs. physiotherapist directed treatment		(Janicki et al. 2009)
Tenotomy		(Chong et al. 2014), (Cosma et al. 2018), (Dinesh et al. 2017), (Hallaj-Moghaddam et al. 2015), (Kuzma et al. 2019), (Little et al. 2019), (Panjavi et al. 2012), (Ramírez et al. 2011), (Willis et al. 2009), (Zhao et al. 2018)
Age at tenotomy		(Chong et al. 2014), (O'Halloran et al. 2015)
Local vs. general anesthesia		(Tuhanioğlu et al. 2018)
Type of brace		(Chong et al. 2014), (Cosma et al. 2018), (Limpaphayom and Sailohit 2019)

tary data). Studies not included in the meta-analysis were in line with these results.

In addition, Kuzma et al. (2019) found no association for employment, but Mootha et al. (2011) found a significant association between lower socioeconomic status and higher recurrence rates. Age of parents was not associated with recurrence rates.

Treatment factors

23 studies investigated the association between 15 treatment-related factors and clubfoot recurrence (Table 5). 5 factors were assessed in a meta-analysis.

2 studies investigated the association between additional stretching as part of the post-corrective treatment and recurrence rates and were included in the meta-analysis. Not applying additional stretching increased the odds for recurrence 32-fold (CI 10–101; 70% risk; Figure 5A, see Supplementary data), exceeding the threshold value for clinical significance. The meta-analysis on the number of casts included 3 out of 11 studies and showed 3.5 times higher odds of recurrence when > 5 casts were applied during Ponseti treatment (CI 1.6–7.8; 78% risk; Figure 5B, see Supplementary data), exceeding the threshold value for clinical significance. Similarly, a higher age at completion of casting was associated with a higher recurrence rate (Kuzma et al. 2019). However, the remaining 8 studies did not find associations between the number of casts and recurrence rates. The initial age at start of treatment (> 3 months), whether other (conservative) treatment preceded Ponseti treatment or whether tenotomy was performed (Figure 5C, D, E, see Supplementary data), were not associated with recurrence rates. This was in line with the additional studies included in the qualitative synthesis, except for one study showing a significant association for the initial age at start of treatment (Willis et al. 2009).

Based on the qualitative analysis only, changing casts every 7 days compared with every 5 days and shorter duration of bracing were associated with an increased recurrence rate. Inconclusive results were found for the duration of follow-up treatment and cast duration. Other treatment-related factors showed no clear association with recurrence rates.

Behavioral factors

Only brace compliance was identified as a behavioral factor (Table 6). 21 articles investigated the association between brace compliance and recurrence rates, of which 17 were included in meta-analysis. The odds of clubfoot recurrence increased 10 times when patients were non-compliant with the bracing protocol (CI 5–21; prediction interval: 0.6–180; 91% risk; Figure 6), see Supplementary data, exceeding the threshold value for clinical significance. The studies not included in the meta-analysis did not report an association between non-compliance and recurrence rates. Average compliance rate was 89% in those studies that did not report associations, ranging from 70% to 100% in the recurrent group, whereas average compliance rate was 66% in those studies reporting significant associations, ranging from 0% to 40% in the recurrent group.

Table 6. Overview and outcome of studies: presented behavioral factors for risk of recurrence

Treatment factor	Significant association	Not significant association
Brace non-compliance	(Abdelgawad et al. 2007), (Avilucea et al. 2009), (Dinesh et al. 2017), (Haft et al. 2007), (Limpaphayom and Sailohit 2019), (Mahan et al. 2017), (Mootha et al. 2011), (Morcuende et al. 2004), (Morcuende et al. 2005), (Panjavi et al. 2012), (Ramírez et al. 2011), (Sangiorgio et al. 2016), (Sangiorgio et al. 2017), (Zhao et al. 2018)	(Chong et al. 2014), (Cosma et al. 2018), (Gelfer et al. 2014), (Kang and Park 2015), (Kuzma et al. 2019), (Little et al. 2019), (Vo and Huynh 2016)

Discussion

This systematic review and meta-analysis aimed to establish clinically relevant factors associated with the risk of clubfoot recurrence after initial correction with the Ponseti method. In line with our hypothesis, brace non-compliance and poor evertor muscle activity were strong prognostic factors for clubfoot recurrence. In addition, children requiring > 5 casts and who did not receive additional stretching had a higher recurrence risk. These 4 risk factors all exceeded the threshold for clinical significance. Furthermore, small associations, not exceeding the clinical significance threshold, were identified between the incidence of recurrence and the severity of the initial deformity as measured with the Dimeglio scoring system as well as lower education level and non-marital status of the parents. However, prediction intervals could only be computed for brace compliance, and these were wide, implying large heterogeneity between studies. Scientists and clinicians should therefore use the estimated OR and risk ratios with caution when predicting recurrence rates in future patient populations.

In line with the proposed pathomechanism of clubfoot recurrence, evertor muscle activity and brace non-compliance were identified as strong prognostic factors for clubfoot recurrence. This data suggests that those patients with high compliance rates and good evertor muscle function are able to oppose potentially reoccurring or persisting deforming medial ankle–foot joint forces after initial correction and prevent recurrence. In line with this idea is our finding that adding stretching to the standard bracing protocol significantly reduces recurrence risk.

The addition of stretching to the bracing protocol was examined in 2 of the included studies following different protocols and showing moderate risk of bias. Limpaphayom and Sailohit (2019) asked parents to perform stretching exercises twice a day for 20 minutes, including passive range of motion of the involved ankle–foot joints and squatting exercises after walking age. 30 children completed this program, of which 8 experienced a clubfoot recurrence. In the group not completing the stretching program, 3 out of 4 children experience a recurrence. Panjavi et al. (2012) asked parents to perform dorsiflexion and abduction stretches 3 times a day, for 10 to 15 minutes. 95 feet completed this stretching program, and only 3 recurrences were documented, while of the 34 feet not completing the program, 21 recurrences were diagnosed. Even though stretching is not part of the standard Ponseti treatment protocol, this data suggests that stretching might be a promising method to reduce recurrence rates when added to the standard Ponseti treatment. However, current evidence is still limited and more high-quality experimental studies are required to provide clinical treatment recommendations.

Our data suggests that clinical assessments of evertor muscle function seem valid to identify children unlikely to experience a recurrence as long as they comply with the bracing regimen. However, clinical assessments of evertor muscle activity do not seem sensitive enough to accurately identify those children in need of additional treatment to prevent clubfoot recurrence. Little et al. (2019) reported that about 30% of the children unable to evert their ankle joint immediately after casting did not experience clubfoot recurrence. This is surprising, as one could expect that an inability to evert the ankle would lead to excessive inversion during functional activities such as walking and on the long-term recurrence of clubfoot deformity. We propose 2 main reasons for this seemingly contradictory finding.

First, clinical assessments of evertor muscle activity require (voluntary) activation of isolated muscle groups in a static, sitting position. Functional activities such as unperturbed walking are rhythmic and muscle coordination is largely automatized (Dominici et al. 2011, Yang et al. 2019, Bizzi and Ajemian 2020). The possibility exists therefore, that even though children are unable to evert their ankle joint in a static position, they are still able to control ankle–foot joint motion during functional activities such as walking. Second, clinically assessed evertor muscle activity is subjective and some children, especially at this young age, might not understand or have difficulties in following the instructions of the clinician, leading to inaccurate estimates of evertor muscle function. To better identify children in need of additional intervention to prevent clubfoot recurrence, current clinical assessments of evertor muscle function might be complemented with objective and instrumented measurements (e.g., instrumented gait analysis).

Next, we assumed that more severe initial deformities underlie higher congenital deforming forces and are asso-

ciated with a higher recurrence risk. However, our analysis revealed inconclusive findings. The meta-analysis revealed a small but statistically significant association between Dimeglio scores and recurrence rates, whereas the qualitative analysis and analysis on the Pirani scores did not reveal significant associations. The Dimeglio and Pirani scoring systems are widely used and accepted tools to assess clubfoot severity, plan treatment progression, and inform parents of the expected treatment course (Flynn et al. 1998, Wainwright et al. 2002). However, our data and previous studies question their clinical validity in predicting recurrences. In addition, even though radiographic assessments of ankle–foot joint mobility might improve objectivity of joint mobility assessments we did not identify a clear association between radiographic assessments of dorsiflexion range of motion or the lateral tibio-calcaneal angle and recurrence rates. Our findings are in line with previous studies reporting only moderate to poor correlations between Dimeglio and Pirani scores and the number of required cast changes or the need for additional surgery (Chu et al. 2010, Agarwal and Gupta 2014, Gao et al. 2014, Fan et al. 2017). These findings might imply that manual and radiographic assessments of joint mobility and subjective scoring systems of disease severity are not sensitive enough to accurately quantify disease severity and categorize children based on recurrence risk or expected treatment outcome (Dyer and Davis 2006, Cosma and Vasilescu 2015).

Another potential measure of disease severity is the number of required cast changes to correct the initial deformity (Haft et al. 2007, Chong et al. 2014, Zhao et al. 2018). Our data supports the assumption that more severe deformities require more cast changes to achieve correction, provided these were properly executed. In particular, those children who received > 5 cast changes during Ponseti treatment should be monitored more closely to prevent recurrence.

Finally, analyses of demographic factors revealed an association between educational level and marital status of the parents and recurrence rates. The assumption is that parents with lower education levels have more difficulty understanding the importance of preventive bracing and that single parents have less time for caregiving and treatment due to work obligations negatively affecting compliance rates (Dobbs et al. 2004, Avilucea et al. 2009, Mootha et al. 2011). Assuring that parents understand the importance of bracing and providing different sources of information on various educational levels is a potential strategy to improve compliance and reduce recurrence risk. In some cases, sensor-based monitoring might support parents to comply with the bracing regimen (Sangiorgio et al. 2016).

We identified 2 main aspects requiring improvement in future studies to better identify children with recurrence risk. First, future studies should aim to use more objective and possibly instrumented assessments to establish the exact relationship between musculoskeletal factors and recurrence risk. Second, there is a need for consensus on the definition of recurrent clubfoot deformities. Clubfoot recurrence or relapse is currently defined as either the reappearance of physical qualities of a clubfoot, the need for further treatment after Ponseti treatment or dynamic supination movement while walking (Hosseinzadeh et al. 2019, Thomas et al. 2019). This lack of consensus on a definition impairs comparison between studies, quantification of severity of recurrent deformities, and identification of recurrence risk factors (Gelfer et al. 2019).

The main limitation of this systematic review is that not all included studies were part of the meta-analysis due to a lack of reporting of absolute values. This may have influenced the results and might in part explain the contradictory findings for the Dimeglio score. Furthermore, all included studies demonstrated risk of bias. Alongside this, the average 3-year follow-up period is considered to be too short, because recurrence rates peak around 5 years post initial correction (Stouten et al. 2018). Future studies should incorporate longer follow-up periods (> 5 years) and use randomized controlled, blinded study designs (Wallace et al. 2019).

Conclusion

To conclude, brace non-compliance and poor evertor muscle activity have been identified as main recurrence risk factors and it is therefore important that these be closely monitored during clinical follow-up of clubfoot patients. More experimental evidence is required to conclude whether adding stretching to the standard Ponseti treatment protocol is safe and if it should be added for further reductions in recurrence risk.

HS, CG: designed search strategy literature search, performed literature search, study selection, assessment of literature quality, performed data extraction and statistical analysis, writing, and revision of manuscript. SM, MS: study design, additional support for study selection, interpretation of the results, revision of manuscript. ATB: clinical interpretation of the results, revision of the manuscript.

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Acta thanks Jiri Chomiak and Klaus Dieter Parsch for help with peer review of this study.

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Supplementary data

Appendix 1: Search string PubMed

("Clubfoot"[Mesh] OR clubfoot[tw] OR club-foot[tw] OR clubfeet[tw] OR club-feet[tw] OR talipes equino varus[tw])
AND
("Recurrence"[Mesh] OR relapse[tw] OR recurren*[tw] OR Reoccurren*[tw])
AND
(Ponseti[tw] OR ponseti method[tw] OR ponseti technique[tw] OR ponseti cast*[tw])

Appendix 2: Reference group for categorical and continuous outcomes

Dimeglio score: Severe/Very Severe, i.e., ≥ 10
Pirani score: Severe, i.e., > 4
Education level parents: ≤ high school
Income: < $20,000
Insurance: private
Marital status parents: not married
Sex: male
Laterality: bilateral
Number of casts: > 5
Initial age at start treatment: > 3 months

Appendix 3. Risk of bias assessment of included studies

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Abdelgawad et al. (2007)															
Avilucea et al. (2009)	+	+	+	+	?	?	+	-	?	+	+	+	?	n.a.	S
Brazell et al. (2019)	+	?	+	+	?	?	+	+	+	+	+	+	+	n.a.	M
Chong et al. (2014)	+	+	-	+	?	?	+	-	?	+	+	+	+	n.a.	C
Clarke et al. (2011)	+	?	+	+	?	?	+	+	?	+	+	+	+	n.a.	M
Cosma et al. (2018)	+	+	?	+	?	+	+	-	+	+	-	+	+	n.a.	C
Dinesh et al. (2017)	+	?	-	-	?	?	+	-	+	+	-	+	+	n.a.	C
Gelfer et al. (2014)	+	+	+	+	?	+	+	-	+	+	+	+	+	n.a.	S
Haft et al. (2007)	+	?	+	+	?	?	+	-	+	+	+	-	+	n.a.	C
Hallaj- Moghaddam et al. (2015)	+	+	+	-	?	?	+	-	+	+	+	+	+	n.a.	C
Hosseinzadeh et al. (2016)	+	?	+	+	?	?	+	+	+	+	+	+	?	n.a.	M
Janicki et al. (2009)	+	+	+	+	?	?	+	-	+	+	+	+	+	n.a.	S
Jochymek and Peterková (2019)	+	?	-	-	?	?	+	+	+	+	+	+	+	n.a.	C
Jochymek and Turek (2018)	+	?	-	-	?	?	+	+	+	+	-	+	+	n.a.	C
Kang and Park (2015)	+	?	+	+	+	?	+	+	+	+	+	+	+	n.a.	M
Kuzma et al. (2019)	+	+	+	+	?	+	+	-	+	-	+	-	+	n.a.	C
Limpaphayom and Sailohit (2019)	+	+	+	+	?	?	+	?	+	+	+	+	+	n.a.	M
Little et al. (2019)	+	+	+	+	?	?	+	-	+	+	+	+	+	n.a.	S
Liu et al. (2018)	+	?	+	+	?	?	+	-	+	+	+	+	+	n.a.	S
Mahan et al. (2017)	+	?	+	+	?	?	+	-	+	+	+	-	+	n.a.	S
Mootha et al. (2011)	+	+	+	?	?	?	+	?	+	+	+	+	+	n.a.	M
Morcuende et al. (2004)	+	+	+	+	?	?	+	?	+	+	+	+	+	n.a.	M
Morcuende et al. (2005)	+	+	?	+	?	?	+	?	+	+	+	+	+	n.a.	M
O'Halloran et al. (2015)	+	+	+	+	?	?	+	+	+	+	+	+	+	n.a.	M
Panjavi et al. (2012)	+	?	+	+	+	?	+	?	+	+	+	+	+	n.a.	M
Ramírez et al. (2011)	+	+	+	+	+	-	+	-	+	+	+	+	+	n.a.	C
Sangiorgio et al. (2016)	+	?	?	+	?	+	+	+	+	+	+	-	+	n.a.	S
Sangiorgio et al. (2017)	+	?	+	+	?	+	+	-	+	+	+	-	+	?	C
Shabtai et al. (2015)	+	?	+	?	?	?	+	?	+	+	+	+	+	n.a.	M
Tuhanioğlu et al. (2018)	+	?	+	-	?	?	+	+	+	+	+	+	+	n.a.	S
Vo and Huynh (2016)	+	+	+	+	+	?	+	-	+	+	+	+	+	n.a.	S
Willis et al. (2009)	+	+	-	-	?	?	+	?	+	+	+	+	+	n.a.	Cr
Zhao et al. (2018)	+	?	+	+	?	?	+	-	+	+	+	+	+	n.a.	S
Zionts et al. (2014)	+	?	+	+	?	?	+	?	+	+	+	+	+	n.a.	M

Key: "low risk" (+), "high risk" (-), or "unclear" (?); n.a. not applicable; risk of bias: M = moderate, S = serious, C = critical.

Selection
- A. Valid recruitment of participant
- B. Similar groups based on age
- C. Follow-up > 2 years

Detection
- D. Recurrence explicit and objective defined
- E. Recurrence measurements valid and reliable
- F. Recurrence outcome blindly determined from prognostic factors
- G. Prognostic factors explicit and objectively described
- H. Measurements prognostic factors valid and reliable
- I. Measurements of prognostic factors done at same moment for all participants

Attrition
- J. Follow-up sufficient (> 80% followed)
- K. Measurements of prognostic factors done for appropriate amount of participants of population (n > 30)
- L. All participants included in final analyses

Reporting
- M. Statistical analysis correct
- N. Prognostic model developed and validated
- O. Overall risk of bias judgment

Table 1. Study characteristics of included studies

First author (year)	Study type	A	B	C	D	E	F	G
Abdelgawad (2007)	Retrospective cohort	C	T: 65 (99)	–	14	–	2–3 yrs	FAO n.d., 3 mo 23 h/day → night and nap-time for 3–4 yrs
Prognostic factors:	Brace compliance							
Avilucea (2009)	Prospective cohort	S	T: 100 (138)	T: 59	25	A,B	28 mo (25–34)	FAO n.d., 3 mo 23 h/day → night and nap-time for 3–4 yrs
Prognostic factors:	Brace compliance, income, marital status parents, insurance, education level parents, native American ethnicity, initial age at start of treatment, sex, and initial Pirani score							
Brazell (2019)	Retrospective prognostic	M	T: 53	T: 70	25	A,B	≥ 2 yrs	FAO n.d., median bracing time = 2.4 yrs (interquartile rang = 1.9–3.4)
Prognostic factors:	Initial Dimeglio score, initial age at start treatment, sex, and laterality							
Chong (2014)	Prospective comparative	C	T: 30	T: 80 R: 75 N: 82	27	A, B	19 mo (3–41)	Mitchell shoes + a dynamic or static bar
Prognostic factors:	Number of casts, follow-up time, sex, laterality, tenotomy, age of tenotomy, ethnicity, brace compliance, type of brace, and age of caregivers							
Clarke (2011)	Retrospective cohort	M	T: 50 (75)	T: 82	32	A,B	> 2 yrs	Boots-on-bar, with Piedro boots Brace protocol n.d.
Prognostic factors:	Laterality, sex, and initial Dimeglio score							
Cosma (2018)	Prospective comparative	C	R: 23 (33) [a] N: 19 (28) [a] C: 22	R: 65 N: 63	19	C	–	Ponseti bar, Markell shoes or Dobbs bar Bracing protocol n.d.
Prognostic factors:	Joint laxity, initial age start treatment, initial Pirani score, tenotomy, type of brace, and brace compliance							
Dinesh (2017)	Prospective cohort	C	T: 25 (38)	T: 72	5	–	21 mo (12–24)	Steenbeek FAO 3 mo 23 h/day → night and nap-time
Prognostic factors:	Brace compliance, initial Pirani score, initial age at start of treatment, number of casts, and tenotomy							
Gelfer (2014)	Retrospective cohort	S	T: 38 (59)	T: 74	16	C	30 mo (13–62)	FAO n.d., 3 mo 23 h/day → 12–14 h/day for 4 yrs
Prognostic factors:	Evertor muscle activity after casting, initial Pirani score, number of casts, initial age at start of treatment, and brace compliance							
Haft (2007)	Retrospective cohort	C	T: 51 (73)	T: 65	41	C	35 mo (24–65)	Open-toed, high-top, straight-last shoes attached to Denis Browne bar. 3 mo 23 h/day → night and nap-time till age of 2 yrs
Prognostic factors:	Brace compliance, ethnicity, initial Pirani score, number of casts, initial age at start of treatment, and family history							
Hallaj-Moghaddam (2015)	Prospective cohort	C	T: 85 (85)	T: 69 R: 68 N: 70	29	–	2 yrs	Denis Browne brace 6 mo full time → part time for 3 yrs
Prognostic factors:	Sex, initial age at start treatment, mother's age, accompanied by other deformities, walking age, number of casts, initial Dimeglio score, and tenotomy							
Hosseinzadeh (2016)	Retrospective cohort	M	T: 101 (148)	T: 69	28	B	3.5 yrs (2–7.5)	Denis Browne bars 3 mo full time → part time for 3 yrs
Prognostic factors:	Dorsiflexion							
Janicki (2009)	Retrospective cohort	S	T: 120 (171) [b]	T: 72 P: 71 S: 76	T: 16 P: 14 S: 26	A, B	≥ 2 yrs	Open-toed, high-top, straight-last shoes attached to Denis Browne bar bracing till the age of 4
Prognostic factors:	Surgeon (S) vs. physiotherapist (P) directed treatment							
Jochymek (2019)	Prognostic comparative	C	T: 47	T: 64	11	–	13 (6) mo	FAO n.d., Brace protocol n.d.
Prognostic factors:	Initial Pirani score and initial Dimeglio score							
Jochymek (2018)	Prospective cohort	C	T: 23	T: 65	9	–	13 (4) mo	Denis Browne brace with plastic ankle foot orthosis. Brace protocol n.d.
Prognostic factors:	Severity of talar dysplasia							
Kang (2015)	Retrospective cohort	M	T: 82 (125) R: – (38) Sagittal R: – (28)	T: 77	30	C, or sagittal relapse < 5° of ankle DF	4 (2) yrs	Denis Browne brace + massage 3 mo 23 h/day → part time during day and night-time till the age of 3
Prognostic factors:	Lateral tibio-calcaneal angle, laterality, sex, initial age at start of treatment, initial Dimeglio score, dorsiflexion, and brace compliance							
Kuzma (2019)	Retrospective cohort	C	T: 42 (64)	R: 58 N: 71	40	A, B	5 yrs	Denis Browne brace or switch to Michell-Ponseti brace 3 mo 23 h/day→ part time (14–16 h/day) till the age of 3
Prognostic factors:	Age at end of casting, duration of the casting, Switching braces, initial age at start of treatment, number of casts, brace compliance, initial Dimeglio score, sex, tenotomy, race, and caregiver characteristics							
Limpaphayom (2019)	Retrospective	M	T: 34 (52)	R: 64 N: 65	27	C	2.3 (1.1) yrs	Denis Browne brace (fixed) or articulated Dobbs bar + additional stretching 3 mo 23 h/day → 3 mo for 18–23 h/day → 12–18 h till the age of 4
Prognostic factors:	Brace compliance, initial age at start of treatment, sex, initial Dimeglio score, additional stretching, and type of brace							

Table 1 continued

First author (year)	Study type	A	B	C	D	E	F	G
Little (2019)	Prospective longitudinal	S	T: 104 (172)	T: 71 R: 68 N: 72	19	C	62 mo (41–71)	FAO n.d., bracing till the age of 4 yrs
Prognostic factors:	Evertor muscle activity after casting, initial age at start of treatment, sex, initial Pirani score, number of casts, tenotomy, and brace compliance							
Liu (2018)	Retrospective cohort	S	T: 90 (131)	T: 80	17	A,B,C	5 yrs (4–8)	FAO 3 mo full time → 16–18 h/day till age of 2 → 14–16 h/day till age of 4
Prognostic factors:	Brace compliance and initial age at start treatment							
Mahan (2017)	Retrospective cohort	S	T: 308 (447)	T: 65 R: 57	24	A,B	8.0 (3.0) yrs	Denis Browne brace or Mitchell brace Cohort born before 2006 till the age of 2 yrs Cohort born after 2006 till age of 4 yrs
Prognostic factors:	Brace compliance, brace duration							
Mootha (2011)	Retrospective cohort	M	T: 86 (146) R: – (20) N: – (108)	T: 63	16	B	4 yrs (2–7)	Denis Browne brace 1 yr > 16 h/day → night-time 3 yrs
Prognostic factors:	Socioeconomic status, brace compliance, and initial age at start of treatment							
Morcuende (2004)	Retrospective cohort	M	T: 157 (256) [a]	T: 68	10	C	2.2 yrs (0.5–8)	FAO 2–3 mo full time → night and nap-time for 3–4 yrs
Prognostic factors:	Brace compliance, initial age at start of treatment, previous unsuccessful treatment at another institution, and number of casts needed							
Morcuende (2005)	Retrospective cohort	M	T: 230 (319) [a] R 5-day group: 11 R 7-day group: 25	T: 67	16	C	–	FAO 2–3 mo full time → night and nap-time for 3 yrs
Prognostic factors:	Accelerated Ponseti protocol (5–7 days cast changes), initial age at start of treatment, brace compliance, previous treatment, and number of casts needed							
O'Halloran (2015)	Retrospective cohort	M	T: 45 (71)	T: 76	25	A, B	4.6 yrs (2.2–9.5)	FAO n.d., 2–3 mo full time → 16 h/day till age 3–4 yrs
Prognostic factors:	Dorsiflexion, tibio-calcaneal angle, sex, initial age at start of treatment, age at tenotomy, and length of follow-up							
Panjavi (2012)	Retrospective cohort	M	T: 78 (129)	T: 73 R: 79 N: 74	19	C	25 mo (11–52)	Denis Browne brace 3 mo full time → night-time for 4 yrs + DF stretching exercises 3 x daily for 10–15 minutes
Prognostic factors:	Initial Dimeglio score, brace compliance, sex, family history, stretching, laterality, education level of parents, and tenotomy							
Ramírez (2011)	Retrospective cohort	C	T: 53 (73) [a]	T: 72 R: 56 N: 78	33	A,B,C	48 mo (36–60)	Denis Browne brace 3 mo full time → night-time for 4 yrs
Prognostic factors:	Brace compliance, initial age at start of treatment, sex, laterality, cast changes, tenotomy, initial Dimeglio score, previous treatment, insurance, education level of parents, and family income							
Sangiorgio (2016)	Prospective cohort	S	T: 48 of which 4 not included R: 8 N: 36	T: 77	18	–	–	Mitchell-Ponseti brace 3 mo full time → 16 h/day till age of 1 yr → 14 h/day till age of 2 yrs → 12 h/day till age of 3 yrs → 10 h/day till age of 4 yrs
Prognostic factors:	Measured brace application (with temperature sensors), recommended and reported brace compliance							
Sangiorgio (2017)	Prospective cohort	C	T: 191	T: 70 R: 65 N: 74	49	A,B,C	4.3 yrs (2–10)	Mitchell-Ponseti brace 3 mo 23 h/day → night and nap-time till 4–5 yrs
Prognostic factors:	Initial age at start of treatment, brace compliance, initial Dimeglio score, sex, laterality, marital status and educational status of parents, family income, and insurance							
Shabtai (2015)	Retrospective cohort	M	T: 189 (279)	T: 75	13	B	6.3 yrs (2 –11)	FAO n.d., 9 mo 23 h/day → remove 3 h day → 11–14 mo 18 h/day → sleep + nap-time (12 + 2 h) up to 2 yrs of age
Prognostic factors:	Duration of bracing, walking age, laterality, number of casts, and initial Pirani score							
Tuhanioğlu (2018)	Retrospective comparative	S	T: 57 (85) L: 32 (47) G: 25 (38)	L: 69 G: 64	L: 10 G: 8	–	28 mo	Brace n.d. Brace protocol n.d .
Prognostic factors:	Local (L) vs. general (G) anesthesia							
Vo (2016)	Retrospective cohort	S	T: 101 (142)	–	6.5	C	44 mo (24–117)	Modified brace with poly-axially adjustable shoes 2–3 mo full time → night-time up to 2 yrs of age
Prognostic factors:	Initial correction, latest follow-up results, brace compliance, initial age at start of treatment, and initial Dimeglio score							
Willis (2009)	Retrospective cohort	C	T: 51 (72) [a]	T: 61 R: 36 N: 68	25	–	20 mo (4–48)	Denis Browne brace 3 mo full time → part time for 2 yrs
Prognostic factors:	Tolerance of the brace, initial age at start of treatment, sex, tenotomy, and previous treatment							
Zhao (2018)	Prospective cohort	S	T: 116 (172)	T: 76	26	C	> 2 yrs	Brace n.d., 3 mo full time → 16–18 h/day till age of 2 yrs → 14–16 h/day till age of 4 yrs
Prognostic factors:	Ratio of correction improvement value, initial Pirani score, sex, race, brace compliance, initial age at start of treatment, laterality, number of casts, and tenotomy							

Table 1 continued

First author (year)	Study type	A	B	C	D	E	F	G
Zionts (2014) Prognostic factors:	Prospective cohort Walking age	M	T: 94 [b]	T: 72	15	C + treatment	44 (15) mo	Mitchell-Ponseti brace + heel cord stretch 3 mo 23 h/day → night and nap-time

A. Risk of bias
M = moderate
S = serious
C = critical
B. Number of children (feet)
a = part of sample received treatment prior to initial treatment
b = fiber casting
C. Male sex (%)
D. Recurrence rate (%)
E. Definition of recurrence
A = additional casting
B = additional surgery
C = reappearance of clubfoot deformity components (varus, equinus, cavus, or adductus).
F. Follow-up time (range)/(SD)
G. Bracing protocol
FAO = foot abduction orthosis
→ = followed by
Notes:
T = total group, R = recurrent clubfeet group, N = non-recurrent clubfeet group, C = Control/non-clubfeet.
G = general anesthesia, L = local anesthesia, P = physiotherapist, S = surgeon.
– = no information given, n.d. = not defined, DF = dorsiflexion
yrs = years, mo = months, wks = weeks.

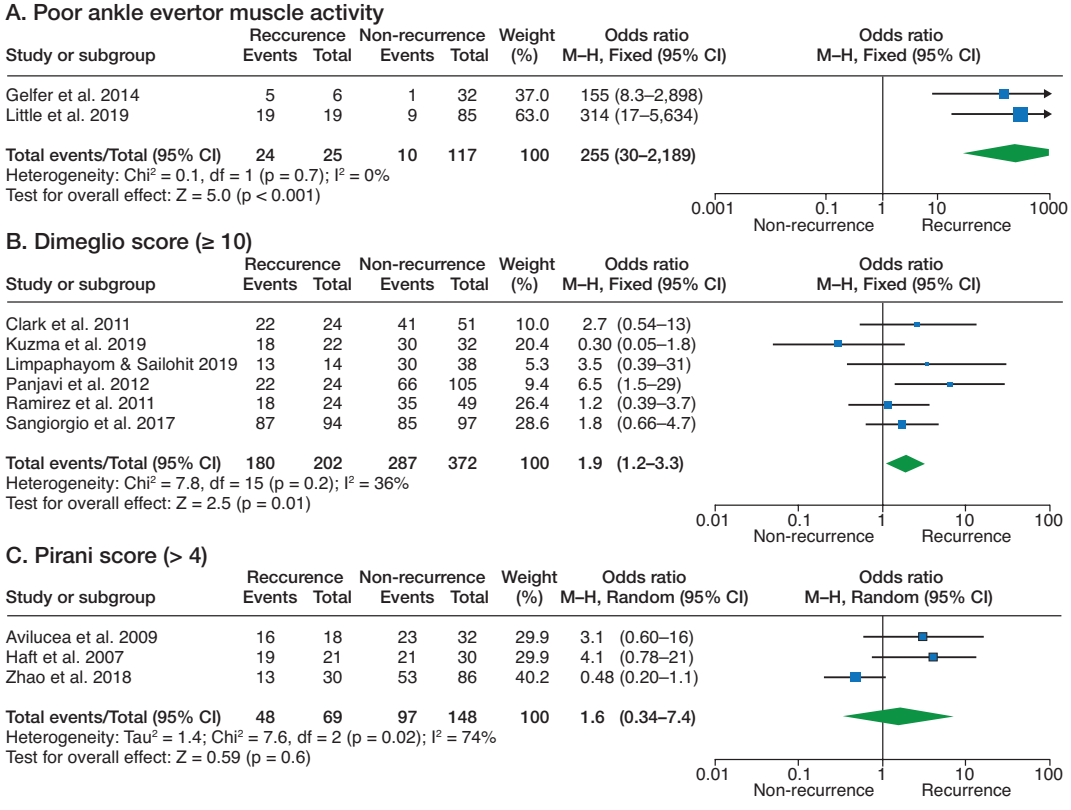

Figure 2. Meta-analyses of musculoskeletal factors.

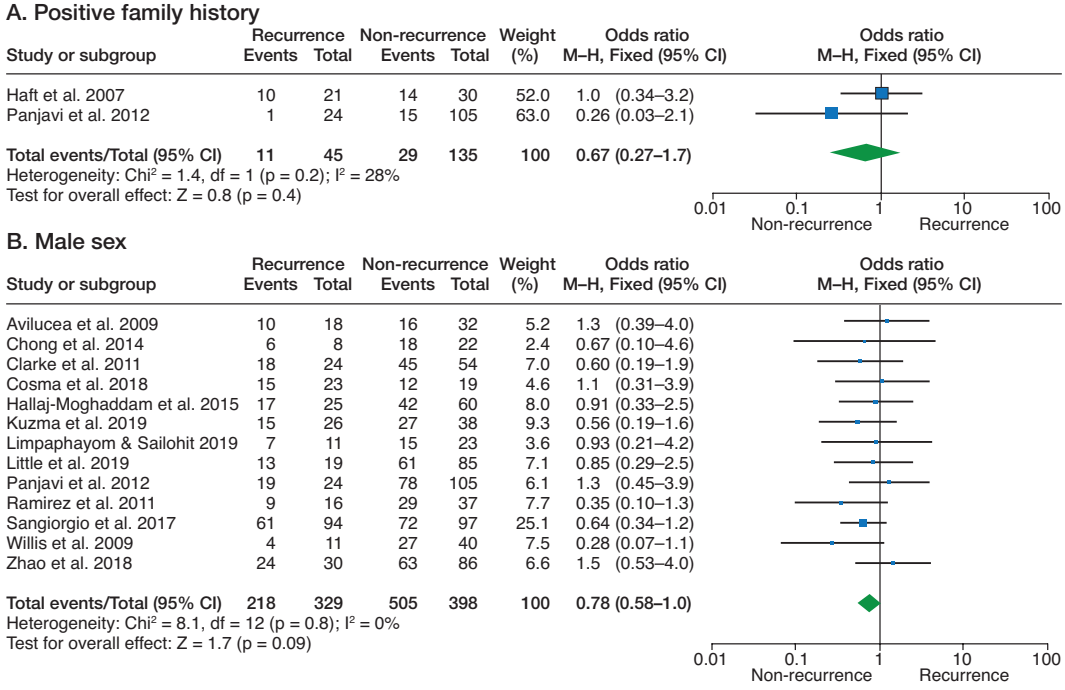

Figure 3. Meta-analyses of genetic factors.

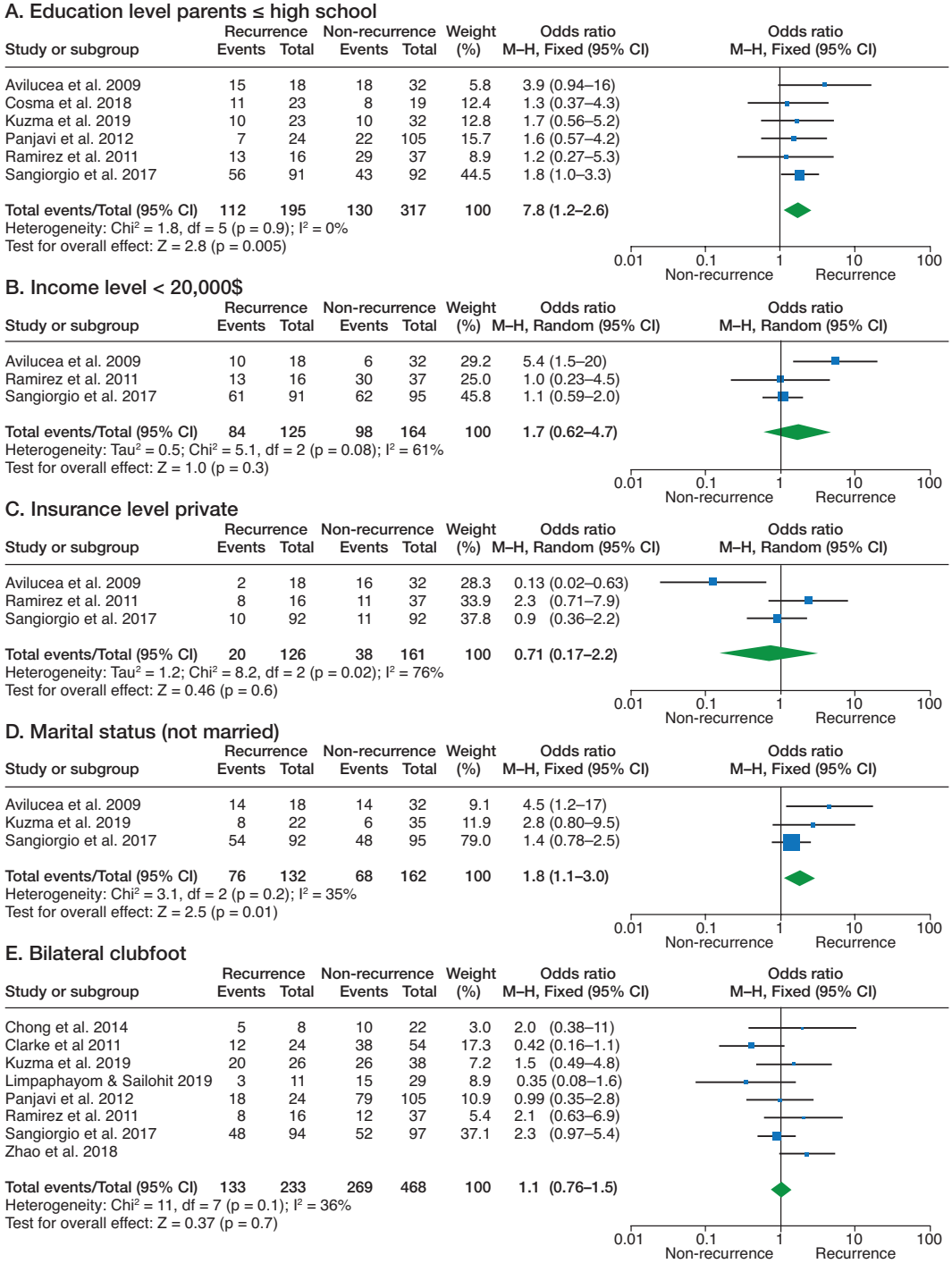

Figure 4. Meta-analyses of demographic factors.

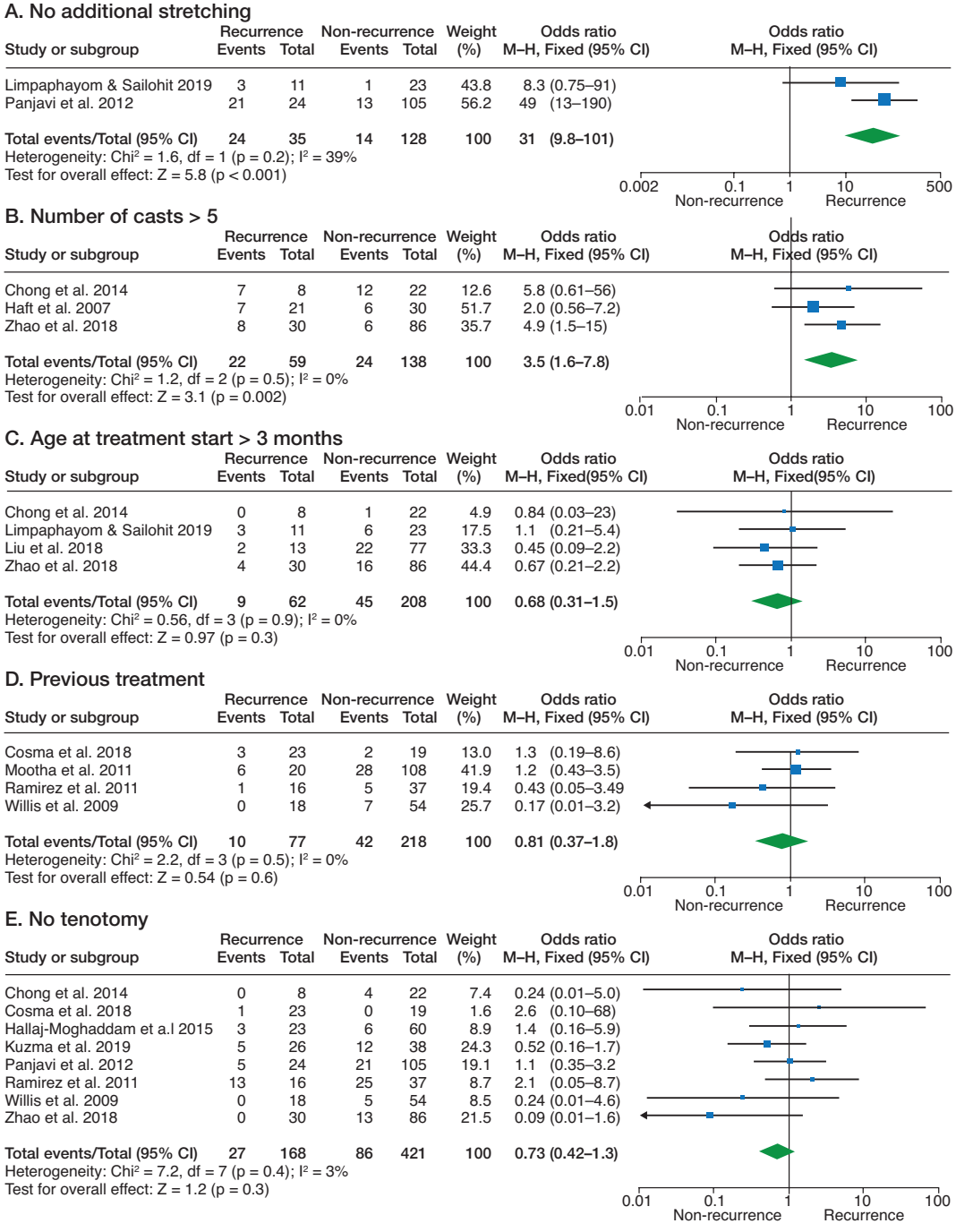

Figure 5. Meta-analyses of treatment related factors.

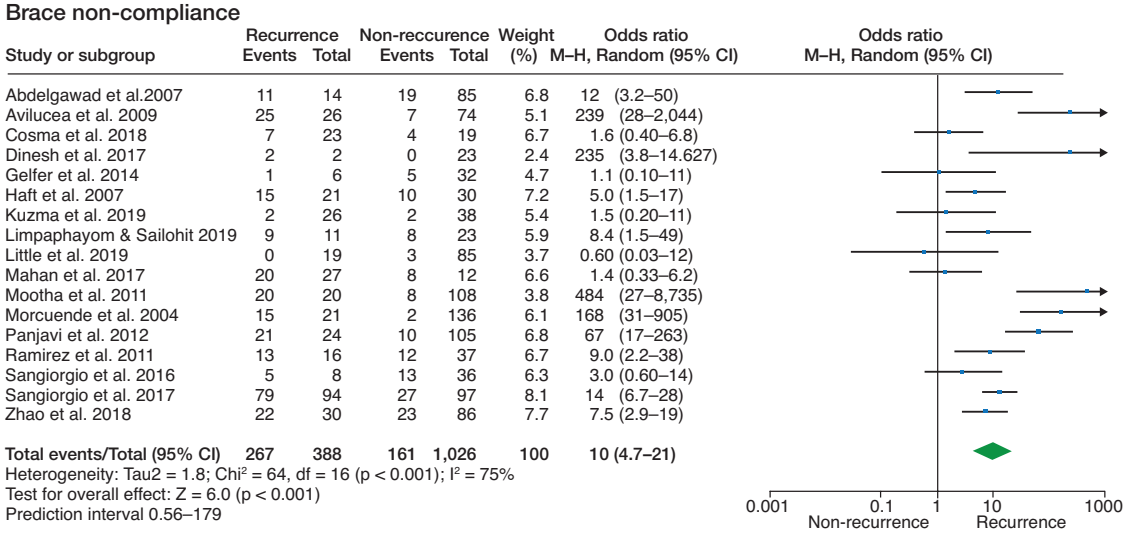

Figure 6. Meta-analyses of risk of recurrence for non-compliance.