Keep calm and carry on testing: a substantive reanalysis and critique of 'what is the evidence for and validity of return-to-sport testing after anterior cruciate ligament reconstruction surgery? A systematic review and meta-analysis'

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Clinicians rely on rigorous systematic reviews to guide practice. We therefore suspect many clinicians will note the results of the 2019 systematic review and meta-analysis by Webster and Hewett, 'What is the Evidence for and Validity of Return-to-Sport Testing after Anterior Cruciate Ligament Reconstruction Surgery? A Systematic Review and Meta-Analysis'.[1] We agree that it is important to evaluate the association between return-to-sport (RTS) test batteries and outcomes after ACL reconstruction. The third review question in Webster and Hewett (2019) is particularly pertinent: 'Is passing RTS test batteries associated with reduced rates of subsequent knee injury (all knee injuries and ACL injury)?'[1] We are authors of several of the original data papers cited in the systematic review, and we are concerned about the study methodology and its conclusions. We highlight major problems with including two studies and present revised analyses that demonstrate the impact these studies had on the conclusions.

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METHODOLOGICAL CONCERNS

First, we question the validity of pooling studies with substantial clinical and methodological diversity.[2] The meta-analysis combined studies where only some athletes returned to sport[3 4] and studies where all, or mostly all, returned to sport;[5–7] studies with skeletally immature patients[7] and studies with elite athletes;[6] and studies where substantially different RTS test batteries were used. Our second concern is that Webster and Hewett[1] did not assess risk of bias, a fundamental precept of systematic review methodology clearly stated in the PRISMA reporting guideline.[8–10] Assessment of study quality (as performed by Webster and Hewett[1]) does not quantify risk of bias.[11] A risk of bias assessment identifies factors within studies that can skew results, and these factors must be considered carefully in the decision to pool data and in the conclusion. Important bias domains for review questions 2 and 3 include (i) study participation, (ii) study attrition, (iii) methods used to ascertain RTS pass status, (iv) outcome (subsequent injury), (v) confounding, and (vi) statistical analysis and reporting.[12]

HOW TWO STUDIES DESIGNED TO ASSESS DIFFERENT RESEARCH CONSTRUCTS IMPACTED CONTRALATERAL ACL INJURY RESULTS

We believe that Webster and Hewett's report of 235% greater risk of contralateral ACL injury among those who passed RTS criteria[1] is an artefact of including two studies that were not designed to answer the same research question as the three other studies in the meta-analysis. In the studies by Sousa *et al*[3] and Wellsandt *et al*,[4] the RTS test results were used to determine when athletes were cleared to return to sport. Early return to sport is among the strongest risk factors for reinjury,[5 13–15] and delaying return to sport in those who initially fail RTS testing is likely to protect them from reinjury. In these two studies,[3 4] reinjuries were reported irrespective of whether the patients returned to sport after RTS testing. The three other studies[5–7] in the meta-analysis represented athletes who returned to sport even if they failed RTS tests (all patients returned to sport in the studies by Kyritsis *et al*[6] and Grindem *et al*,[5] and 39 of 42 patients returned to sport in Graziano *et al*[7]). These patients returned to sport either because of nonadherence to the protocol or because the RTS test battery was not used for sports clearance in the sample. We contend that the clinically relevant question of whether patients should pass RTS tests prior to return to sport cannot be informed by studies where return to sport was delayed if the patient failed the RTS tests[3 4]. Pooling these studies[3 4] in a meta-analysis is therefore inappropriate.

In the study by Sousa *et al*, confounding may also play a large role and is clearly highlighted in the paper's conclusion.[3] Patients who passed RTS criteria in their study were younger, had higher preinjury and follow-up activity levels, and returned to sport earlier.[3] Young age,[16–23] high activity levels,[17 18 22] and early return to sport[5 13–15] are very strong risk factors for second ACL injury; we expect higher injury rates in the 'passed RTS criteria' group than in the older 'failed RTS criteria' group who participated in less knee-demanding sports and had delayed return to sport. The majority (9/16) of the contralateral ACL injuries reported in Webster and Hewett[1] were derived from the Sousa *et al* study,[3] which was the only individual study that showed a higher rate of contralateral ACL injuries in the group that passed RTS tests. This single study accounted for 77% of the weighting for the contralateral ACL injury meta-analysis and heavily influenced the conclusions drawn by Webster and Hewett.[1]

Four of the remaining seven contralateral ACL injuries among the athletes who passed the RTS test in the meta-analysis were derived from the study by Wellsandt *et al.*[4] This study was designed to evaluate estimated preinjury capacity (EPIC) levels as alternatives to limb symmetry indexes, not the association between the established RTS criteria and second ACL injuries. Patients in this study[4] only received RTS clearance after they passed RTS testing,[24] either 6 months after ACLR (the test point reported in Wellsandt *et al*[4]) or at a later time-point after completing additional

Study or Subgroup	Passed RTS criteria Events	Passed RTS criteria Total	Not passed RTS criteria Events	Not passed RTS criteria Total	Weight	Odds Ratio M-H, Random, 95% CI
Graziano 2017	4	37	1	4	9.6%	0.36 [0.03, 4.38]
Grindem 2016	1	18	9	55	13.0%	0.30 [0.04, 2.55]
Kyritsis 2016	12	116	14	42	77.4%	0.23 [0.10, 0.55]
Total (95% CI)		**171**		**101**	**100.0%**	**0.25 [0.12, 0.54]**
Total events	17		24			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0\%$
Test for overall effect: Z = 3.53 (P = 0.0004)

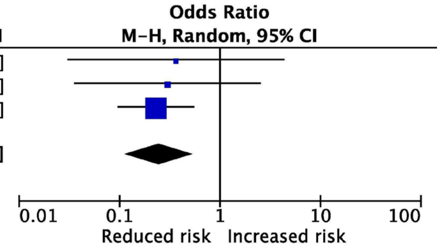

Figure 1 Reanalysis showing the risk for any second ACL injury among those who pass versus fail RTS criteria. M-H, Mantel-Haenszel; RTS, return to sport.

Study or Subgroup	Passed RTS criteria Events	Passed RTS criteria Total	Not passed RTS criteria Events	Not passed RTS criteria Total	Weight	Odds Ratio M-H, Random, 95% CI
Graziano 2017	2	37	1	4	9.0%	0.17 [0.01, 2.49]
Grindem 2016	0	18	8	55	7.6%	0.15 [0.01, 2.75]
Kyritsis 2016	12	116	14	42	83.4%	0.23 [0.10, 0.55]
Total (95% CI)		**171**		**101**	**100.0%**	**0.22 [0.10, 0.48]**
Total events	14		23			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 3.73 (P = 0.0002)

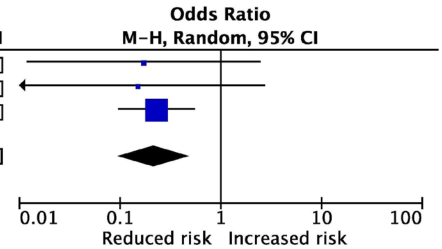

Figure 2 Reanalysis showing the risk for an ACL graft rupture among those who pass versus fail RTS criteria. M-H, Mantel-Haenszel; RTS, return to sport.

rehabilitation. Having no contralateral ACL injuries among those who 'failed' the RTS test battery six months after surgery was not surprising as these patients did not return to sport at that time. Instead, athletes who failed the RTS tests continued rehabilitation and were scheduled for a new test at a later time. This prevents a meaningful comparison because no one *in this specific sample* returned to sport until they passed RTS criteria. As authors, we acknowledge that this information is not explicitly stated in the paper. Had we known the data would be used for another purpose than the original paper, we would have clarified to avoid this misinterpretation.

REVISED ANALYSIS AND INTERPRETATION OF RESULTS

Here we demonstrate how conclusions change when the two studies[3 4] with critically different study designs are excluded from the meta-analysis.

1. In the meta-analysis for *any knee injury*, Sousa *et al*[3] and Wellsandt *et al*[4] were excluded by Webster and Hewett, so their analysis remains unchanged. *Passing RTS test batteries is associated with 72% lower risk of further knee injury* (i.e., ACL injury and other knee injuries, 95% CI: 6% to 96% lower risk, p=0.09).[1]
2. Webster and Hewett[1] reported no significant association (p=0.68) between successfully passing the RTS test and having a lower rate of subsequent ACL injury (ie, graft rupture and/or contralateral ACL injury). However, after excluding the studies by Sousa *et al*[3] and Wellsandt *et al*,[4] those *athletes who passed the RTS criteria had 75% lower odds* (95% CI: 46% to 88% lower odds) *of any ACL injury than those who failed* (p<0.01, figure 1).
3. Webster and Hewett[1] found that those who passed RTS criteria had a 60% lower risk for ACL graft rupture (95% CI 31% to 77%, p=0.003). By excluding the inappropriate studies,[3 4] and pooling remaining data, *there is 78% lower odds of graft rupture in those who passed RTS criteria compared with those who failed* (95% CI: 52% to 90% lower odds, p<0.01, figure 2).
4. By excluding the studies by Sousa *et al* and Wellsandt *et al*,[3 4] there are only four total contralateral ACL ruptures left for analysis (among those who passed or failed RTS criteria). *These numbers are too low to say whether or not passing RTS criteria influences risk of contralateral ACL rupture*.

CONCLUSION

Our reanalysis omits two studies[3 4] with designs that addressed a different research construct than the remaining three and/or have a high risk of bias. We found that compared with patients who fail RTS tests prior to return to sport, athletes who pass RTS test batteries have: (1) a lower risk of (any) knee reinjury, (2) a lower risk of any second ACL injury and (3) a lower risk of ACL graft rupture; (4) no conclusions regarding contralateral ACL injury risk can be drawn due to insufficient data.

More evidence is needed to refine RTS test batteries to provide greater certainty in their ability to facilitate successful RTS. Future meta-analyses should critically evaluate the study design of each potential contributing paper and include a risk of bias assessment. Meta-analyses should also consider the impact of sparse data bias[25] and avoid the Firth penalization when events are 0, as this method can change the direction of the reported association.[26 27]

In future studies, authors should report and/or control for sport level and athletic exposure. Researchers should aim to rigorously evaluate: (1) which tests can help clinicians help athletes return to play successfully, (2) the optimal values for cut-off scores and (3) alternatives to limb symmetry indexes. Importantly, all studies to date are observational, and there is a need for interventional designs (eg, pragmatic trials or site randomisation). Such studies will improve clinicians' understanding of RTS test batteries and, with appropriate implementation, should reduce secondary knee and ACL injuries.

Clinicians *should not fear* an increased risk of contralateral ACL injuries on the basis of the current literature, but *continue to use RTS test batteries* (and appropriate time-frames) to support RTS decision-making.

Correction notice This article has been corrected since it was published Online First. The order of references 5-7 has been updated.

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