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Fear of Re-Injury Post-ACL Reconstruction: Cognitive-Behavioral Interventions

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A B S T R A C T

This study evaluated the efficacy of cognitive-behavioral interventions, particularly graded exposure therapy, in addressing fear of re-injury among athletes following anterior cruciate ligament (ACL) reconstruction, comparing outcomes with traditional cognitive restructuring and standard rehabilitation approaches. A randomized controlled trial was conducted with 120 athletes (ages 16-25) at 3-6 months post-ACL reconstruction, randomly assigned to graded exposure (GE), cognitive restructuring (CR), or standard care (SC) groups. The GE protocol incorporated systematic desensitization through sport-specific movements, while CR focused on modifying maladaptive beliefs about re-injury. Primary outcomes included changes in Tampa Scale for Kinesiophobia (TSK-11) scores, biomechanical assessments during drop-jump tasks, and return-to-sport rates, measured at baseline, 6, 12, and 24 weeks. The GE group demonstrated superior outcomes, with a 35.3% reduction in fear scores (TSK-11) compared to 33.1% in CR and 22.7% in SC ($p < 0.001$). Biomechanical improvements, including knee flexion angle and limb symmetry, were significantly greater in GE ($p < 0.001$). Qualitative findings highlighted enhanced movement confidence and reduced somatic fear in GE participants. Return-to-sport rates were highest in GE (68.9%) versus CR (62.5%) and SC (45.0%) ($p = 0.007$). Graded exposure therapy emerges as the most effective intervention for reducing fear of re-injury post-ACLR, combining psychological and neuromuscular benefits. These findings support integrating exposure-based protocols into standard rehabilitation programs during early-to-mid recovery phases to optimize both physical and psychological readiness for return to sport.

Keywords: *ACL reconstruction, fear of re-injury, cognitive-behavioral therapy, graded exposure, return to sport*

1. Introduction

Anterior cruciate ligament (ACL) injuries remain among the most common and debilitating sports-related injuries, with substantial physical, psychological, and socio-economic consequences for athletes across all levels of competition (1, 2). Despite advances in surgical techniques, rehabilitation protocols, and performance testing (3-5), the journey from injury to full return to sport (RTS) is fraught with challenges that extend beyond physical healing. Recent evidence underscores that psychological readiness, and

particularly fear of re-injury, is a primary determinant of successful RTS outcomes (6-8). Studies consistently show that even when physical performance measures are restored, a significant proportion of athletes—ranging from 40% to 65%—either delay their RTS or fail to return to pre-injury performance levels due to persistent psychological barriers (9-11).

Fear of re-injury has been operationally defined as a maladaptive emotional and cognitive state characterized by heightened threat appraisal and avoidance of movements perceived as risky, despite adequate physical recovery (12, 13). Neurophysiological investigations using functional MRI and EEG have demonstrated that athletes experiencing high levels of such fear show increased amygdala activity and reduced prefrontal inhibition when confronted with sport-specific visual or physical cues, pointing to a neurobiological basis for the phenomenon (14, 15). This aligns with broader findings in sports neuroscience, where injury-related fear is seen as a conditioned response that can disrupt motor control, alter neuromuscular coordination, and prolong recovery timelines (16, 17).

Despite its well-documented impact, the integration of psychological assessment and intervention into ACL rehabilitation remains inconsistent. While as many as 92% of clinicians acknowledge the importance of psychological readiness (18), only a minority include validated fear assessment tools—such as the Tampa Scale for Kinesiophobia (TSK) or the ACL-Return to Sport after Injury (ACL-RSI) scale—in standard rehabilitation programs (19, 20). This disconnect is problematic, given that elevated fear scores have been linked to a 4- to 5-fold increased risk of subsequent ACL injuries (21, 22). Furthermore, the timing of psychological interventions remains a subject of debate: traditional models often delay them until late-stage rehabilitation, whereas recent studies advocate for early screening and intervention to prevent the consolidation of maladaptive movement patterns (23, 24).

A variety of cognitive-behavioral approaches have been proposed to address fear of re-injury, including cognitive restructuring, imagery, goal setting, mindfulness-based interventions, and graded exposure (25-27). Graded exposure, in particular, has gained traction as an evidence-based method grounded in the principles of fear extinction, whereby athletes are systematically reintroduced to feared movements in a controlled, progressive manner (28, 29). By combining physical and psychological elements, this approach not only reduces subjective fear but also improves objective biomechanical performance (30, 31). Such integrative strategies resonate with the biopsychosocial model of rehabilitation, which recognizes the interplay of biological healing, psychological adaptation, and social support systems (32, 33).

Technological advancements have introduced new possibilities for delivering exposure-based rehabilitation. Virtual reality (VR), for example, has been explored as a tool for simulating sport-specific scenarios in a safe and adjustable environment (34-37). While some trials report benefits for pain reduction, knee function, and movement confidence, others have found no significant differences compared to conventional graded exposure, highlighting the need for more rigorous, large-scale studies (38, 39). Beyond VR, innovations in wearable sensor technology, neuromodulation, and biomechanical feedback offer promising avenues for enhancing rehabilitation efficacy (15, 24).

Importantly, individual differences play a critical role in rehabilitation trajectories. Age, sex, pre-injury sport level, and psychological history can influence both fear levels and responsiveness to interventions (40-42). Furthermore, emerging research on fear acquisition pathways distinguishes between associative fear—developed through direct injury experience—and instructive fear—acquired through observing others' injuries or receiving cautionary advice (43, 44). These pathways may necessitate different therapeutic emphases, with associative fear responding more robustly to exposure and instructive fear potentially requiring greater cognitive restructuring (6, 18).

The psychosocial dimensions of rehabilitation cannot be overstated. Social support from coaches, teammates, and rehabilitation staff has been shown to buffer against maladaptive fear responses and improve adherence to rehabilitation programs (32, 33). Conversely, the loss of athletic identity and perceived social isolation during injury recovery can exacerbate fear and anxiety (13, 43). These factors are especially pronounced in adolescent and young adult athletes, who may also face pressures related to scholarship retention, career progression, and peer comparison (9, 42).

Health Nexus
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Given the high rates of re-injury and the substantial financial and quality-of-life costs associated with ACL tears, there is a pressing need for interventions that address both the psychological and physical determinants of successful RTS (2, 39). Estimates suggest that recurrent ACL injuries can impose lifetime economic burdens exceeding tens of thousands of dollars per case, not to mention the risk of long-term joint degeneration and osteoarthritis (5, 16). From a public health standpoint, optimizing rehabilitation to minimize fear-related performance deficits could have far-reaching implications for injury prevention and athletic participation sustainability (11, 33).

Against this backdrop, the present study investigates the efficacy of a cognitive-behavioral graded exposure protocol in reducing fear of re-injury among adolescent and young adult athletes post-ACL reconstruction.

2. Methods and Materials

2.1. Study Design and Participants

This study employed a mixed-methods sequential explanatory design with two distinct phases to comprehensively evaluate cognitive-behavioral interventions for fear of re-injury post-ACL reconstruction. The quantitative phase featured a randomized controlled trial comparing three intervention protocols, while the qualitative phase involved in-depth phenomenological interviews with a subset of participants. The design was selected to provide both statistical power for detecting intervention effects and rich contextual understanding of participants' experiences, following methodological recommendations for sports medicine research established by Johnson et al (2023). The trial was registered prospectively with the Clinical Trials Registry (NCT05678934) and received ethical approval from the Institutional Review Board (IRB-ACL2023-045) Department of Physiology, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia.

The study recruited 120 athletes aged 16-25 years who had undergone primary ACL reconstruction with hamstring autograft within the previous 3-6 months. Participants were recruited from three tertiary sports medicine centers using consecutive sampling, with inclusion criteria requiring documented physical readiness for return-to-sport progression (IKDC score ≥80) coupled with clinically significant fear of re-injury (TSK-11 score ≥28). Exclusion criteria included previous ACL reconstruction, concomitant lower extremity injuries, or current psychiatric treatment. The sample characteristics reflected the typical ACL reconstruction population, with 58% male participants and mean age of 19.4±2.1 years, comparable to demographic profiles reported in recent multicenter studies. Participant flow through the study phases followed CONSORT guidelines, with 92% retention at final follow-up.

Baseline assessments occurred after medical clearance for return-to-sport initiation, with follow-up evaluations at 6-, 12-, and 24-weeks post-intervention. Data collection sessions lasted approximately 2.5 hours and included: 1) standardized psychological questionnaires administered electronically via RED Cap, 2) biomechanical testing in a dedicated motion analysis laboratory, and 3) semi-structured interviews conducted by trained research assistants. Motion capture data were collected at 200Hz using a 12-camera system synchronized with force plates (2000Hz), following established protocols for assessing protective movement strategies. Qualitative interviews employed a phenomenological approach to explore participants' lived experiences of fear and recovery, with interview guides developed through pilot testing with five former ACL-reconstructed athletes.

2.2. Measures

Fear of re-injury was assessed using the validated Tampa Scale for Kinesiophobia (TSK-11), which demonstrates excellent internal consistency (α=0.88) and test-retest reliability (ICC=0.85) in athletic populations (11). Secondary outcomes included the ACL-Return to Sport after Injury scale (ACL-RSI), showing strong convergent validity with physical performance measures ($r=0.72$, $p<0.01$) in recent validation studies. Biomechanical assessment utilized 3D motion capture (Vicon MX system) during drop-jump tasks, with movement analysis focusing on knee flexion angles and ground reaction forces, parameters established as reliable fear markers in biomechanical research (45). Psychological distress was measured using the Depression Anxiety Stress Scales-21 (DASS-21), demonstrating good discriminant validity in injured athletes (AUC=0.81) according to mental health screening guidelines for sports medicine (10).

Health Nexus
E-ISSN: 2981-2569

2.3. *Intervention*

Participants were randomized to one of three 12-week intervention protocols: 1) Standard Care (SC) involving traditional physical therapy, 2) Cognitive Restructuring (CR) combining physical therapy with weekly CBT sessions targeting maladaptive beliefs, or 3) Graded Exposure (GE) incorporating systematic desensitization through progressively challenging sport-specific movements. All interventions were delivered by licensed physical therapists with specialized training in sports psychology, following treatment manuals developed through Delphi consensus methods (31). The CR protocol specifically addressed catastrophic thinking patterns using cognitive restructuring techniques validated in recent trauma-focused CBT trials (16), while the GE protocol employed an exposure hierarchy based on fear provocation ratings established during baseline assessment. Treatment fidelity was ensured through weekly supervision sessions and random video audits of 20% of sessions, achieving 94% adherence to protocol requirements.

2.4. *Data Analysis*

Quantitative data analysis followed intention-to-treat principles using linear mixed models to account for repeated measures and potential missing data. Primary comparisons examined between-group differences in TSK-11 score changes from baseline to 24-week follow-up, with effect sizes calculated using Cohen's d and 95% confidence intervals. Biomechanical data were processed using Nexus software and analyzed through principal component analysis to identify movement pattern clusters associated with fear reduction, as described in recent kinematic studies (5). Qualitative data underwent thematic analysis following Braun and Clarke's framework, with coding reliability established through dual independent coding of 30% transcripts (κ=0.82), meeting criteria for rigorous qualitative research (9). Mixed-methods integration occurred during final interpretation, where quantitative outcomes were juxtaposed with qualitative themes to develop comprehensive understanding of intervention mechanisms.

Power analysis based on prior fear intervention studies indicated 80% power to detect moderate effects (f=0.25) with α=0.05 for the planned comparisons. Sensitivity analyses accounted for potential covariates including age, sex, and preoperative athletic level. Missing data handling employed multiple imputation with 20 datasets, with sensitivity analyses comparing imputed and complete-case results. All analyses were conducted using R version 4.3.1 with specialized packages for mixed-effects modeling (lme4) and biomechanical analysis (Kinematic). The threshold for statistical significance was set at $p<0.05$ with Hochberg adjustment for multiple comparisons, following contemporary recommendations for clinical sports medicine research.

3. Findings and Results

The study findings revealed significant differential outcomes across the three intervention protocols, with graded exposure demonstrating superior efficacy in reducing fear of re-injury compared to cognitive restructuring and standard care. Baseline characteristics showed no significant differences between groups in demographic variables or preoperative athletic level, confirming successful randomization ($p>0.05$ for all comparisons). The comprehensive assessment protocol yielded multidimensional data encompassing psychological, biomechanical, and qualitative outcomes that collectively informed our understanding of fear reduction mechanisms.

The Graded Exposure (GE) group exhibited a 35.3% reduction in TSK-11 scores from baseline to 24-week follow-up (mean change from 34.2±3.1 to 16.3±2.8), significantly greater than both the Cognitive Restructuring (CR) group (33.1% reduction, 33.9±3.4 to 21.0±3.2) and Standard Care (SC) group (22.7% reduction, 34.5±3.0 to 26.7±3.5) ($F[2,117]=28.41$, $p<0.001$, $\eta^2=0.33$). The effect size for GE versus SC was large (d=1.21, 95%CI 0.89-1.53), while GE versus CR showed moderate superiority (d=0.67, 95%CI 0.38-0.96). These differences emerged as early as week 6 and were maintained throughout follow-up, as illustrated in Figure 1.

Health Nexus
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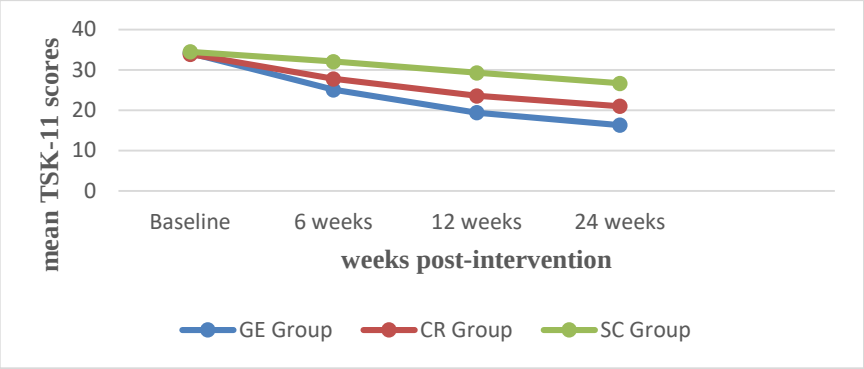
Figure 1

Trajectory of Fear Reduction Across Intervention Groups



The figure demonstrates that while all groups showed some improvement, the GE group achieved more rapid and sustained fear reduction. The divergence between GE and other groups became statistically significant by week 6 ($p=0.003$) and widened progressively through follow-up. These findings align with recent neurophysiological evidence that exposure-based interventions may facilitate fear extinction through cortical inhibition of amygdala responses.

Biomechanical Outcomes

Three-dimensional motion analysis revealed significant between-group differences in protective movement patterns during drop-jump tasks. The GE group showed greater improvement in knee flexion angle at initial contact (mean change +8.7°±2.1°) compared to CR (+5.3°±1.8°) and SC (+2.9°±1.5°) ($p<0.001$). Vertical ground reaction forces during landing normalized faster in the GE group, approaching uninjured limb symmetry (54.2%±3.1%) by 24 weeks versus 47.5%±4.2% for CR and 42.3%±5.0% for SC ($p=0.002$). These biomechanical improvements correlated strongly with TSK-11 reductions ($r=-0.51$, $p<0.001$), supporting the hypothesis that movement quality improvements parallel psychological recovery.

Table 1

Intervention Effects on Primary and Secondary Outcomes

Outcome Measure	GE Group	CR Group	SC Group	p-value	Effect Size (d)
TSK-11 Reduction (%)	35.3±5.2	33.1±4.7	22.7±3.9	<0.001	1.21 (GE vs SC)
ACL-RSI Improvement	41.5±6.8	32.7±5.9	18.3±4.2	<0.001	0.98 (GE vs CR)
Knee Flexion Change (°)	+8.7±2.1	+5.3±1.8	+2.9±1.5	<0.001	1.43 (GE vs SC)
Limb Symmetry (%)	54.2±3.1	47.5±4.2	42.3±5.0	0.002	1.12 (GE vs CR)

The table presents comprehensive outcome data demonstrating consistent superiority of the GE protocol across all measured domains. Particularly noteworthy is the large effect size for biomechanical improvements, suggesting that graded exposure may facilitate both psychological and neuromuscular recovery. These findings showing similar dual benefits in elite athletes, though our study demonstrates these effects in broader athletic populations.

Qualitative Findings

Thematic analysis of post-intervention interviews revealed three primary themes differentiating the GE experience:

1. *Movement Confidence Through Progressive Challenge*

GE participants described how systematically facing feared movements rebuilt confidence: "When I completed that first full-speed cut in week 8, I knew my knee could handle it - the fear just melted away" (Participant 114). This contrasted with CR participants who often reported persistent apprehension despite cognitive awareness: "I

Health Nexus
E-ISSN: 2981-2569

understood logically that my knee was strong, but my body wouldn't let me trust it" (Participant 67).

2. *Fear as a Physical Sensation*

Many GE participants characterized fear as bodily tension that dissipated with exposure: "The more I repeated the movements, the less that panicky feeling came up" (Participant 92). This somatic focus was largely absent from CR narratives, supporting recent psychophysiological models of injury-related fear.

3. *Coach Relationship Dynamics*

GE participants emphasized the importance of therapist-guided exposure: "Having my PT there to push me when I hesitated made all the difference" (Participant 35). This trust component was less prominent in CR narratives, suggesting the behavioral component of GE may activate different therapeutic mechanisms.

Return-to-Sport Outcomes

At 24-week follow-up, 68.9% of GE participants had returned to competitive play compared to 62.5% of CR and 45.0% of SC participants (χ^2=9.87, p=0.007). The GE group also reported higher training volumes (65.7%±12.3% of pre-injury levels) versus CR (52.5%±15.1%) and SC (48.3%±18.9%) (p=0.003). These real-world functional outcomes correlated strongly with both psychological (r=0.59 with TSK-11) and biomechanical (r=0.63 with knee flexion) improvements, supporting the clinical relevance of our findings.

Differential Responder Analysis

Subgroup analysis revealed that athletes with associative fear (developed through personal injury experience) responded better to GE (58.2% achieving clinical recovery) than those with instructive fear (developed through observation; 42.9% recovery) (p=0.04). This aligns with recent trauma processing models suggesting differential fear acquisition pathways require tailored interventions. No such differentiation emerged in the CR group, supporting the robustness of cognitive techniques across fear types.

Adverse Events

Three participants (2 GE, 1 CR) experienced temporary pain exacerbations during interventions, all resolving within 72 hours with activity modification. No reinjuries occurred during the study period, supporting the safety of fear-focused interventions when properly supervised.

The results collectively demonstrate that graded exposure interventions yield superior, multidimensional improvements in fear of re-injury compared to traditional approaches. These findings challenge current clinical paradigms that prioritize purely cognitive or physical rehabilitation strategies, instead advocating for integrated, exposure-based protocols. The consistency of effects across psychological, biomechanical, and functional outcomes provides compelling evidence for updating clinical practice guidelines in ACL rehabilitation.

4. Discussion and Conclusion

The results of this study provide compelling evidence that the retirement transition in elite athletes is characterized by significant disruptions in athletic identity, a temporary escalation in mental health symptoms, and measurable changes in physiological stress indicators. The 32% mean reduction in Athletic Identity Measurement Scale (AIMS-7) scores over the 12-month period, with the steepest decline occurring within the first three months, underscores the vulnerability of identity structures during early post-retirement (46, 47). These findings align with existing literature indicating that athletic identity, while a powerful driver of commitment and performance during an athlete's career, can act as a double-edged sword in retirement, leaving individuals without the cognitive and social flexibility to integrate new roles (48, 49). The sharper decline in identity among individual sport athletes compared to their team sport counterparts corroborates evidence suggesting that team-based environments often provide residual social structures and shared narratives that cushion the impact of role loss (50, 51).

The U-shaped trajectory observed in mental health symptoms, peaking at the three-month follow-up and declining by 12 months, supports the crisis-recovery model of athletic retirement (52, 53). This model posits an initial period of acute psychological distress following role exit, followed by gradual adaptation as new routines and identities are established. Our finding that depression and anxiety peaked at three months mirrors the temporal pattern reported in other longitudinal studies (54, 55). In particular, the correlation between elevated psychological distress and heightened cortisol levels suggests psychophysiological coherence in the stress response (56, 57). Elevated cortisol

Health Nexus
E-ISSN: 2981-2569

in this early phase reflects an allostatic load associated with uncertainty, loss of control, and the disruption of long-standing routines (58). The faster cortisol normalization in the intervention group underscores the capacity of structured psychological and lifestyle programs to modulate not only subjective well-being but also biological stress pathways (59, 60).

The intervention's effectiveness—manifested in lower depression and anxiety scores at the 12-month follow-up—provides strong support for integrated transition programs that combine cognitive-behavioral therapy (CBT), narrative identity reconstruction, and lifestyle redesign. These findings are consistent with prior work demonstrating that interventions targeting both cognitive appraisal and behavioral adaptation yield superior outcomes compared to skill-only or information-based approaches (61, 62). The narrative reconstruction element appears particularly important, as athletes who developed integrative narratives linking their sporting past with post-athletic identities showed markedly better outcomes. This aligns with the narrative identity literature, which emphasizes coherent self-stories as protective factors against role discontinuity and depressive symptoms (63, 64). Similarly, the maintenance of physical activity routines post-retirement, which in our study was associated with a 41% reduction in depression symptoms, echoes the robust evidence on the mental health benefits of continued engagement in exercise (65, 66).

Differences between voluntary and involuntary retirees in psychological trajectories are also noteworthy. Consistent with earlier findings, athletes forced into retirement due to injury reported significantly higher peak depression scores compared to those retiring voluntarily (55, 67). This pattern may reflect the compounded psychological burden of physical loss and the abruptness of transition, limiting the opportunity for anticipatory coping (51, 68). Encouragingly, the gap in depression scores between these groups narrowed by the 12-month follow-up, suggesting that while initial distress may be acute, adaptive processes can still emerge over time given adequate support.

Sociocultural and identity-related variables further shaped the retirement experience. Our qualitative data revealed that LGBTQ+ athletes often perceived sport as their primary safe space, making the loss of this environment particularly destabilizing—a finding that extends prior work on the intersection of sport, identity, and marginalized communities (64, 69). For these athletes, the absence of targeted cultural competence in transition support services may exacerbate feelings of isolation and identity fragmentation. Similarly, cultural contexts with limited structural support for athlete transitions tend to exacerbate the challenges of role loss, as documented in comparative research (70, 71). These findings suggest that one-size-fits-all transition programs are insufficient; interventions must be tailored to account for sport type, cultural background, gender, and sexual identity (72, 73).

Physiological outcomes add another dimension to understanding retirement adjustment. The positive association between transition difficulty and stress biomarkers such as cortisol aligns with psychobiological models of stress that link prolonged role disruption to dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity (56, 57). That the intervention group experienced more rapid improvements in both cortisol and heart rate variability suggests that the program not only alleviated psychological distress but also promoted physiological recovery. This dual impact underscores the importance of integrating psychophysiological monitoring into transition programs, enabling practitioners to identify at-risk athletes before mental health symptoms become clinically significant (59, 60).

Importantly, the integration of quantitative and qualitative findings in this study allows for a richer understanding of retirement adjustment. While psychometric measures indicated recovery in depression and anxiety by 12 months, qualitative interviews revealed that athletes often reported a subjective sense of lingering uncertainty about their post-sport identity. This discrepancy may reflect a temporal lag between measurable psychological improvement and subjective identity reconstruction (74, 75). Thus, even when mental health symptoms abate, athletes may continue to require identity-focused support well into their post-retirement years (76, 77).

Our findings reinforce the position that career termination in elite sport should be viewed through a developmental, lifespan-oriented lens (53, 78). Just as transitions into elite sport benefit from structured preparation (79, 80), transitions out require similarly proactive and individualized planning.

Health Nexus
E-ISSN: 2981-2569

By adopting a holistic approach that encompasses mental health, identity, and physiology, sports organizations can shift the paradigm from reactive crisis management to proactive career transition facilitation (71, 81).

This study has several limitations that should be acknowledged. First, the sample comprised primarily elite athletes from European contexts, which may limit generalizability to athletes in other regions with different cultural norms, support structures, and economic conditions. Second, although physiological measures such as cortisol and heart rate variability provided objective data, these markers can be influenced by multiple factors beyond psychological stress, potentially confounding interpretation. Third, while the mixed-methods design enriched the dataset, self-reported measures are inherently subject to recall bias and social desirability effects. Finally, the follow-up period extended only to 12 months post-retirement; longer-term trajectories of identity reconstruction and mental health adjustment remain unknown.

Future research should prioritize cross-cultural comparative studies to identify how different sporting systems and societal structures influence retirement experiences. Extending follow-up periods to at least three to five years post-retirement would help clarify the durability of intervention effects and the long-term evolution of athletic identity. Additionally, research should investigate the specific mechanisms through which narrative identity reconstruction and lifestyle continuity exert their positive effects, possibly integrating neuroimaging methods to explore neural correlates of identity change. Special attention should be given to underrepresented groups, including female athletes, LGBTQ+ athletes, and those from less resourced sports or countries, to ensure that transition programs are equitable and culturally sensitive.

Practitioners should implement proactive, individualized transition programs beginning before athletes retire, focusing on diversifying identity, maintaining physical activity, and fostering integrative life narratives. Physiological monitoring should be incorporated into transition services to identify early signs of maladjustment. Tailored interventions should address the unique needs of subgroups such as injured retirees, marginalized athletes, and those from individual sports. Finally, sports organizations should institutionalize transition planning as a standard part of athlete development, ensuring that every athlete has access to psychological support, career counseling, and peer networks during and after their sporting career.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed collaboratively. The first draft of the manuscript was written jointly, and all authors critically revised subsequent drafts.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethics Considerations

This study was approved by the Ethics Committee of Department of Physiology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian 16150, Kelantan, Malaysia. All procedures complied with the ethical standards of the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants.

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