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ORIGINAL ARTICLE

The Dose–Response Relationship of an Exercise-Based Injury Prevention Program: A Secondary Analysis of a Randomized Controlled Trial on Athletics (Track-and-Field) Athletes Over a 39-Week Follow-Up

Spyridon Iatropoulos[1] | Pierre-Eddy Dandrieux[1,2,3] | Laurent Navarro[2] | David Blanco[4] | Pascal Edouard[1,5]

[1]Université Jean Monnet Saint-Etienne, Lyon 1, Université Savoie Mont-Blanc, Inter-University Laboratory of Human Movement Biology (EA 7424), Saint-Etienne, France | [2]Mines Saint-Etienne, Univ Lyon, Univ Jean Monnet, INSERM, U 1059 Sainbiose, Centre CIS, Saint-Etienne, France | [3]Institute of Interdisciplinary Exercise Science and Sports Medicine, Medical School Hamburg, Hamburg, Germany | [4]Physiotherapy Department, Universitat Internacional de Catalunya, Barcelona, Spain | [5]Department of Clinical and Exercise Physiology, Sports Medicine Unit, Faculty of Medicine, University Hospital of Saint-Etienne, Saint-Etienne, France

Correspondence: Spyridon Iatropoulos (spyridon.iatropoulos@univ-st-etienne.fr) | Pascal Edouard (Pascal.edouard@univ-st-etienne.fr)

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ABSTRACT

Despite exercise-based injury prevention programs (EIPPs) being widely researched and used, several randomized controlled trials (RCTs) have failed to show their protective effect on injury risk. This is potentially due to underappreciating the EIPP dose–response relationship, by not controlling the analysis for the injuries sustained during the early EIPP implementation period, before the EIPP becomes efficacious. To determine the dose–response relationship of EIPP by controlling for the effects of injuries sustained before it became efficacious. We conducted a secondary analysis of an RCT analyzing the EIPP efficacy in athletics over a 39-week follow-up on 840 athletes, by including only those with 100% response rate. We controlled the statistical analyses for a range of lengths of early EIPP implementation period by either excluding the athletes with early injuries (i.e., exclusion approach) or adjusting for the early injuries' effects (i.e., inclusion approach). We estimated the EIPP's dose–response relationship by measuring the EIPP's effect at each length of the controlled period. When we considered no early controlled period, the EIPP showed no effect (OR = 0.85 [95% CI: 0.67–1.09]; $p = 0.209$). However, both exclusion and inclusion approaches showed that the EIPP effect increased significantly after 5–6 weeks of controlled period. This relationship plateaued at 7–12 weeks of controlled period, peaking at 10 weeks with the exclusion approach (OR = 0.28 [95% CI: 0.16–0.48]; $p < 0.001$), and 7 weeks with the inclusion approach (OR = 0.37 [95% CI: 0.25–0.55]; $p < 0.001$). Acknowledging the dose–response relationship of EIPPs could help researchers to design and analyze RCTs and practitioners to plan EIPP implementation timely.

Trial Registration: ClinicalTrials.gov Identifier: NCT03307434

David Blanco and Pascal Edouard contributed equally to this article.

1 | Introduction

Given the high prevalence, incidence, and burden of sports injuries, numerous injury prevention strategies have been developed and tested, with exercise-based injury prevention programs (EIPPs) being the most studied [1]. Several randomized controlled trials (RCTs) and meta-analyses reported the efficacy of different EIPPs to reduce injury risk [2–8]. However, for some EIPPs reportedly efficient in meta-analyses [6–8], there were some individual RCTs testing these EIPPs which did not report any efficacy to reduce the injury risk [9–14]. Also, RCTs evaluating other proposed EIPPs have shown no efficacy [15–19]. Such reported inefficacy of EIPPs could be attributed to factors related to (i) the program development (e.g., not targeting the sport-specific physical demands, absence of progressive loading in the exercises, insufficient musculoskeletal loading), (ii) the program implementation (e.g., suboptimal compliance, too short intervention period), and/or (iii) the statistical analysis (e.g., perhaps not isolating the effect of the EIPP) [8, 20–23].

Similarly to training for performance [24, 25], EIPPs may need to be performed for a sufficient period of time before they become efficient [26]. This corresponds to the concept of the dose–response relationship, originating from pharmacological and epidemiological sciences and recently appearing in sport sciences [27–29]. It associates the magnitude of any defined biological outcome with regard to the quantity of a causative agent, in which an organism or a population is exposed [30]. Such agents can be pharmaceutical drugs, environmental toxic factors, a bout of exercise, or in our case, performing an EIPP. Similarly, biological outcomes can be any measurable anatomical, physiological or biochemical parameter, or a health problem (i.e., injury). The dose of EIPP implementation can be quantified by its frequency, duration, or a combination of both. Focusing on the duration of the dose, when response is defined as a structural adaptation at the tissue level, the dose–response relationship of certain EIPPs (e.g., Nordic exercise for the hamstring muscles, isometric plantar flexion for the Achilles tendon) has already been described [31–34]. However, to our knowledge, no information exists on the dose–response relationship when the response is an injury-related outcome. This dose–response relationship has often been underappreciated in RCTs evaluating the impact of EIPPs on injury risk, with the injury data collection starting simultaneously with the intervention period (i.e., EIPP implementation). In these cases statistical analyses were based on the entire intervention period [14, 16–19, 35, 36]. To our knowledge, only two RCTs considered separating the two periods and started the period of injury data analysis after the end of the EIPP implementation period [37, 38].

Not differentiating between the EIPP implementation and the injury data collection periods during RCT analyses can lead to three different potential problems. First, injuries occurring during the first weeks after the EIPP implementation (named "early-sustained injuries") could not have been related to the efficacy of the EIPP. Thus, including these injuries in the statistical analysis could introduce a *dilution effect* which could reduce the EIPP's effect estimation (Figure 1A). Second, given that previous injuries can act as a risk factor for new injuries [39, 40], the athletes who sustained an injury during this early period may carry an additional risk of reinjury during the later follow-up

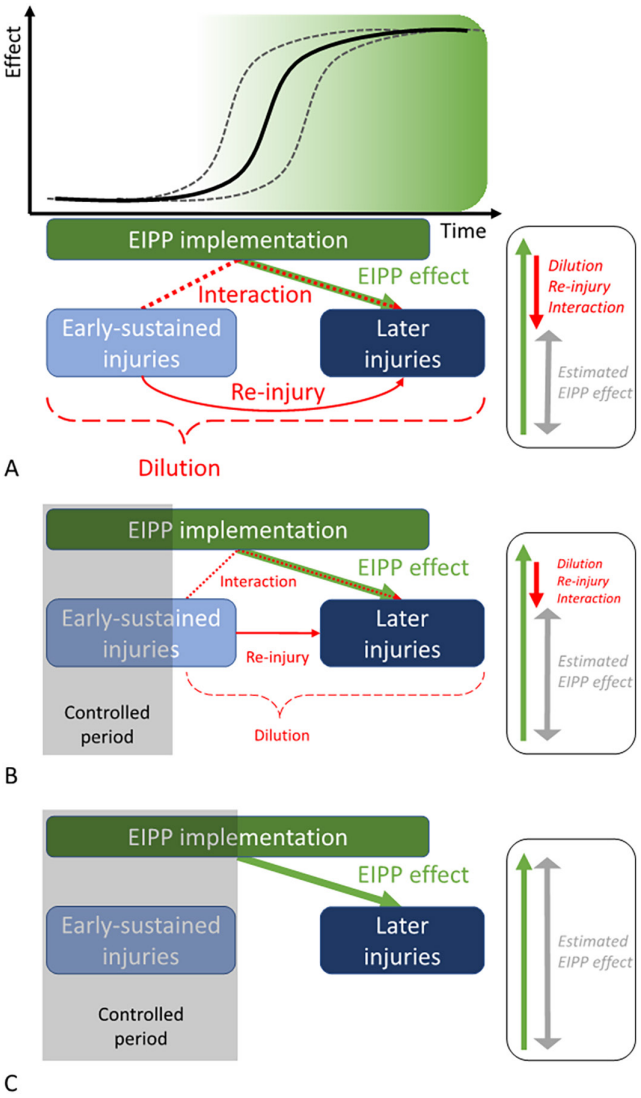

FIGURE 1 | The dose–response relationship of exercise-based injury prevention programs and its influence on the estimated effect of an EIPP based on the length of the analysis period. (A) Including the period before the EIPP reaches efficacy in analysis introduces interfering effects (dilution, reinjury, and interaction effects) which reduce the estimated effect. Partial (B) or complete (C) control of this period results in partial or complete suppression of these effects, respectively, allowing for better measurement of the EIPP isolated effect.

(i.e., *reinjury effect*) (Figure 1A). Third, there could also be an *interaction effect* of early-sustained injuries with the elicited adaptations of the EIPP, either due to decreased compliance with the EIPP, to abstaining from training while injured, or to biological modifications at the tissue level (Figure 1A). Although the latter has not been researched, there is some evidence showing how previously injured muscles may be less adaptable to strength training later [41]. Consequently, controlling for these three aspects when analyzing the results of RCTs evaluating the efficacy of an EIPP could allow to better estimate its effect.

The exact length of the early period that needs to be controlled between the implementation of an EIPP and the start of the analysis is usually unknown and may depend on the characteristics of the EIPP. Generally, the optimal strategy to estimate the effect

of the EIPP could be to start analyzing data of injuries right after the EIPP is considered to have caused the desired adaptations, while controlling for the injuries that occurred before that moment (Figure 1C). Consequently, if the length of the controlled period is shorter than that necessary for the EIPP to become efficacious, the undesirable effects of the three aforementioned problems would not be fully suppressed (Figure 1B). For this reason, exploring the relationship between the length of the controlled period and the efficacy of the EIPP is key to estimate the dose–response relationship of the EIPP. In this study, we aimed to determine the dose–response relationship of an EIPP by exploring the optimal length of the early EIPP implementation period that needed to be controlled for, in order to minimize the impact of the three aforementioned effects (i.e., *dilution*, *reinjury*, and *interaction*) on the estimation of the EIPP's efficacy.

2 | Methods

2.1 | Study Design, Population, and Overall Procedure

We conducted a secondary analysis of the PREVATHLE RCT, which involved a population of competitive athletics (track-and-field) athletes and took place during the athletics season 2017–2018 [18]. This RCT was reviewed and approved by the Committee for the Protection of Persons (CPP Ouest II—Angers, number: 2017-A01980-53). In that study, included athletes, aged 15–40 years old and irrespective of their injury history, were randomly allocated to an intervention or a control group (allocation ratio 1:1). Athletes in the intervention group were asked to incorporate a customized EIPP (the Athletics Injury Prevention Programme—AIPP) at least twice a week into their unaltered training [18]. The control group did not make any changes to their training [18]. The results of the PREVATHLE study showed that the AIPP intervention did not reduce the injury risk for any injury-related outcome [18]. For more information about the PREVATHLE RCT protocol and results, see Edouard et al. [18].

In this secondary analysis, we followed a similar approach to Edouard et al. [18] while accounting for the impact of the dilution, reinjury, and interaction effects of early-sustained injuries defined above (Figure 1). We repeated the analysis for all possible lengths (from 0 to 29 weeks) of the early AIPP implementation period for which these effects were controlled. The remaining period was considered as the analysis period of injury data collection. The dose–response relationship of the AIPP was estimated by using the length of the controlled period as the duration of AIPP implementation and the AIPP effect on injury risk as the response.

2.2 | Patient and Public Involvement

There was no patient or public involvement.

2.3 | Equity, Diversity, and Inclusion Statement

All athletes registered at the international athletics championships were included in this study without any restriction based on sex, race/ethnicity/culture, socioeconomic level, or representation from marginalized groups. Apart from sex and discipline, no other sociodemographic data were considered in the analysis and interpretation of results. The research team included two junior researchers, one senior physician, and two senior researchers, from a variety of disciplines (sports medicine, sports science, sports epidemiology, physical medicine and rehabilitation, data science), and three different countries in Europe (France, Spain, Greece).

2.4 | Data Collection, Injury Definition, and Outcome

At the start of the study, all athletes reported baseline information about their anthropometric profile, training, and injury history during the previous season. During the study's follow-up of 39 weeks, athletes were emailed at the start of every week and were asked to provide a report that asked for information about (i) the amount and type of training and competition during the previous week for athletic and nonathletic sport activities, (ii) the compliance with the AIPP, and (iii) any possible injury complaints. An injury complaint was defined as: "a pain, physical complaint or musculoskeletal lesion sustained by an athlete during participation in athletics training or competition, regardless of whether it received medical attention or its consequences with respect to impairments in connection with competition or training" [18]. Injury complaints were further characterized by their impact on training and/or competition: (i) unrestricted participation, (ii) partially restricted participation, (iii) completely restricted participation [18]. The last two categories of injury complaints were considered together as injury complaints leading to participation restriction (ICPR) [18]. The outcome used for the present analyses was the ICPR, as per the PREVATHLE study [18]. Given that our analysis was based on a week-by-week basis, a weekly outcome was deemed appropriate so that comparisons over different lengths of the analysis period would be valid. Had we considered an outcome calculated over the entire period, it would have been heavily influenced by the length of the analysis period. Thus, we specifically considered as outcome the presence or absence of ICPR for each athlete at every given week (i.e., weekly ICPR).

2.5 | Data Processing

Two common ways to control for the effect of a variable in statistical analysis are (i) to stratify the sample according to this variable and analyze each stratum separately or (ii) to adjust appropriately for this variable in the statistical model [42]. Here, to control for the dilution, reinjury, and interaction effects of early-sustained injuries, two distinct approaches were thus employed: (i) an exclusion approach, where the analysis was focused only on the subset of participants who remained injury-free throughout the controlled period, and (ii) an inclusion approach, where the analysis was conducted on all participants but was adjusted to the presence or absence of an early-sustained injury (Figure 2). Both approaches were applied in a two-step process (Figure 2).

The first step, which was identical in both approaches, was to determine the length of the controlled period. Therefore, the

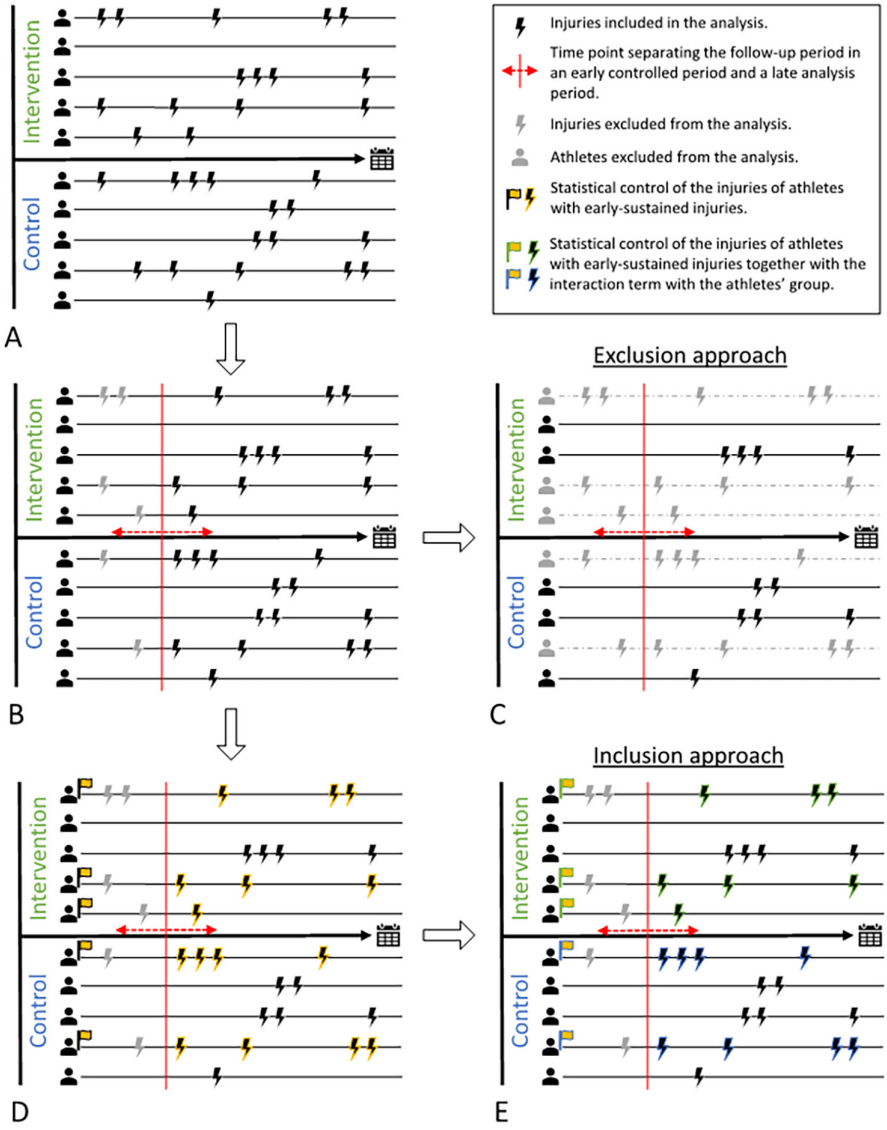

FIGURE 2 | Schematic step-by-step representation of data processing from the uncontrolled analysis (A) to the exclusion (C) and inclusion (E) approaches, where all three effects were controlled. The intermediate steps, where either the dilution effect (B) or the dilution and reinjury effects (D) of early-sustained injuries were only controlled, are also presented.

analysis only considered injuries sustained during the later period. Consequently, this step aimed to control for the dilution effect (Figure 2B). We performed one analysis for each possible length of the controlled period from 0 to 29 weeks, and not up to 39 weeks, because the analysis period would shrink to less than 10 weeks if we controlled for more than 29 weeks, leading to under-powered analyses, and it was expected that the full efficacy would have been achieved much sooner than 29 weeks according to meta-analyses [3, 43].

The second step differed between the two approaches. In the exclusion approach, after determining the length of the controlled period, we excluded from the analysis the athletes who had reported at least one ICPR during this period. Consequently, the analysis only considered injuries occurred after the controlled period and by athletes who had remained injury-free in this period. Thus, the estimated AIPP effect would be unaffected by the reinjury and interaction effects and would thus isolate the intervention effect (Figure 2C). In the inclusion approach, after determining the length of the controlled period, we created a new binary variable which reflected whether an athlete had sustained at least one ICPR during the controlled period or not. Then, we added in the statistical analysis this variable to adjust for the reinjury effect (Figure 2D) and its interaction with the group variable (i.e., intervention or control group allocation) to control for the interaction effect (Figure 2E).

2.6 | Statistical Analysis

For each length of the controlled period, a logistic regression model with weekly ICPR as outcome was fitted on the data collected after the controlled period. The independent variables were the same variables as in the primary analysis: (i) the

athlete's allocation (binary variable: intervention or control), (ii) history of ICPR during the previous season (binary variable: yes or no), (iii) the athlete's compliance to the program (continuous variable), and (iv) the athlete's exposure in athletics and training and competition (continuous variable) [18]. At a given week, compliance was calculated as the average of the times the AIPP was performed per week until that week, and exposure was calculated as the average of training and competition duration per week until that week. First, we analyzed the results without a controlled period, which are equivalent to the original PREVATHLE analysis (uncontrolled analysis over the entire 39-week follow-up). Then, we performed the analyses following the inclusion and exclusion approaches. In the exclusion approach we did not adjust further as we had already confined the analysis to the subset of athletes who were injury-free in the controlled period. In contrast, in the inclusion approach, we further adjusted for the presence of early-sustained injuries with and without the interaction term between early-sustained injuries and the group (intervention or control). A summary of the analytical approaches with mathematical formulations is presented in Appendix S1: A. The dose–response relationship of the AIPP could be visually identified by plotting the observed effect relative to the length of the controlled period.

Data processing was conducted using the "Pandas" (v.2.1.4) module [44], and statistical analyses were conducted using the "statsmodels" (v.0.14.1) module [45] of the Python programming language (v.3.12.0) [46]. All effect values were reported as adjusted odds-ratios (OR) with 95% confidence intervals (CI). The level of significance was set at $\alpha = 0.05$.

3 | Results

3.1 | Population

This analysis included 165 athletes (intervention: 68, control: 97) with 100% response rate; in comparison to the 168 athletes included in the primary analysis, three were excluded because of missing data in their baseline questionnaire [18]. The group baseline characteristics are presented in Table 1. Regarding the exclusion approach, the sample size dropped gradually from 165 to 67 (intervention: 27, control: 40) athletes when moving from 0 to 29 weeks of controlled period, respectively (Appendix S1: B). Regarding the inclusion approach, all 165 athletes were included in the analysis regardless of the length of the controlled period.

3.2 | Without Controlled Period: Analysis Over the Entire 39-Week Follow-Up

When the whole injury data collection period was considered in the analysis (and therefore, there was no controlled period), the analysis did not report any significant effect of the AIPP to reduce the ICPR risk (OR = 0.85 [95% CI: 0.67–1.09]; $p = 0.209$) (Figure 3).

3.3 | Controlling for the Dilution Effect

Excluding the early-sustained injuries without further adjustments in the analysis (Figure 2B) brought small improvements in the estimated effect of the AIPP to reduce ICPR risk,

TABLE 1 | Baseline characteristics of the included athletes of each group.

	Intervention group, median (IQR) ($n = 68$)	Control group, median (IQR) ($n = 97$)
Sex	F: 28, M: 40	F: 28, M: 69
Age (years)	33.1 (28.8, 36.9)	30.8 (25.7, 36.8)
Height (cm)	173.5 (167.8, 178)	177 (170, 182)
Bodyweight (kg)	64 (58, 68.3)	67 (60, 72)
Athl. training (h/week)	5 (3.4, 7)	5 (4, 6)
Nonathl. training (h/week)	2 (1, 3.3)	2 (0.5, 3)
Disciplines	Road running: 30	Road running: 36
	Trail: 14	Trail: 20
	Track distances: 15	Track distances: 19
	Combined events: 1	Combined events: 7
	Hurdles: 1	Hurdles: 4
	Jumps: 2	Jumps: 4
	Sprints: 4	Sprints: 3
	Throws: 0	Throws: 2
	Race walking: 1	Race walking: 2
Past season history of injury	No: 36, Yes: 32	No: 51, Yes: 46

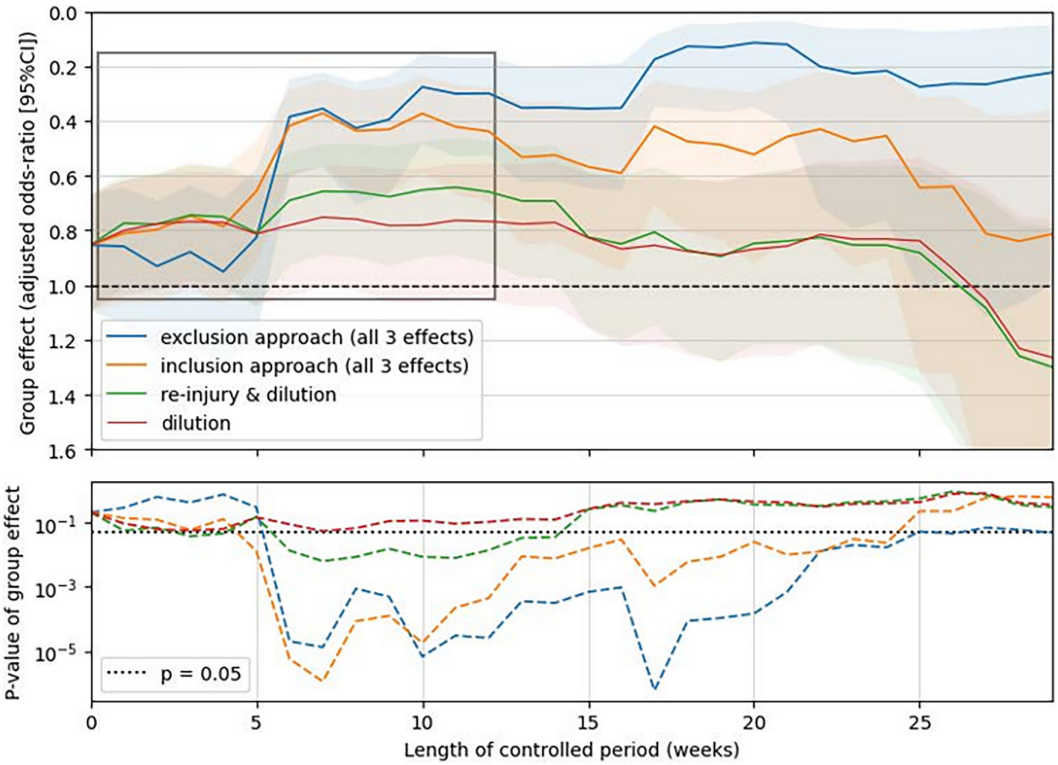

FIGURE 3 | Effect of the exercise-based injury prevention program (i.e., the Athletics Injury Prevention Programme) expressed as adjusted odds-ratio with respect to the length of the early implementation period that was controlled for the three potential effects (i.e., dilution, reinjury, and interaction) of early-sustained injuries. Both the exclusion (Figure 2C) and inclusion approaches (Figure 2E) are presented as well as their intermediate steps of controlling either for the dilution effect (Figure 2B), or the dilution and reinjury effects (Figure 2D). The *p*-values of the effect estimates are also presented for all analyses (significance level = 0.05; black dotted line). The upper left rectangular box highlights the visual representation of the dose–response relationship during the first weeks of implementation (blue and orange lines), where efficacy seemed to emerge after 5–6 weeks of exercise-based injury prevention program implementation, while a plateau of full efficacy was reached from 7 to 12 weeks of implementation.

reaching a maximum effect when the controlled period was 7 weeks long (OR = 0.75 [95% CI: 0.56–1.01]; $p = 0.055$) (Figure 3; Appendix S1: C).

3.4 | Controlling for All Effects—Exclusion Approach

Focusing the analysis on the athletes who were injury-free during the controlled period (Figure 2C) significantly increased the estimated effect of the AIPP to reduce ICPR risk when the controlled period was from 6 to 27 weeks long, with a local maximum being reached at a 10-week long controlled period (OR = 0.28 [95% CI: 0.16–0.48]; $p < 0.001$). Then, it plateaued before reaching an absolute maximum at a 20-week-long controlled period (OR = 0.11 [95% CI: 0.04–0.35]; $p < 0.001$) (Figure 3; Appendix S1: D).

3.5 | Controlling for All Effects—Inclusion Approach

When adjusting only for the dilution and reinjury effects as an intermediate step (Figure 2D), the estimated effect of the AIPP to reduce ICPR risk increased and remained statistically significant when the length of the controlled period ranged between 6 and 14 weeks, reaching a maximum at an 11-week long controlled period (OR = 0.64 [95% CI: 0.46–0.89]; $p = 0.008$) (Figure 3; Appendix S1: E). Adding the interaction term, thus adjusting for all three effects (Figure 2E), had a profound change on the observed effect of the AIPP to reduce ICPR risk, similarly to the exclusion approach. Specifically, at a controlled period of 5–24 weeks long, the observed effect of the AIPP to reduce ICPR risk was statistically significant, reaching a maximum at 7 weeks of control (OR = 0.37 [95% CI: 0.25–0.55]; $p < 0.001$) (Figure 3; Appendix S1: F).

3.6 | Dose–Response Relationship of the AIPP

The visual representation of the dose–response relationship during the first weeks of implementation can be identified in the upper left rectangular box of Figure 3. According to the exclusion approach, the AIPP needed at least 6 weeks of implementation before it became efficacious (OR = 0.38 [0.25–0.6]; $p < 0.001$) reaching a plateau between 7 weeks (OR = 0.36 [0.22–0.57]; $p < 0.001$) and 12 weeks (OR = 0.3 [0.17–0.53]; $p < 0.001$). Similarly, according to the inclusion approach, the AIPP needed at least 5 weeks before it became efficacious (OR = 0.66 [0.47–0.91]; $p = 0.013$) reaching a plateau between 7 weeks

(OR = 0.37 [0.25–0.55]; $p < 0.001$) and 12 weeks (OR = 0.44 [0.28–0.69]; $p < 0.001$) (Figure 3).

4 | Discussion

This secondary analysis determined the dose–response relationship of an EIPP during its first weeks of implementation and showed that the Athletics Injury Prevention Programme (AIPP) [18] would have needed 5–6 weeks of implementation to reach significant efficacy. We reported very similar dose–response relationships by using the two distinct controlling approaches, according to which the maximal efficacy was reached between 7 and 12 weeks of implementation and was estimated to a reduction of injury risk by two-thirds. Remarkably, given the essentially different data manipulation strategies between the two approaches (Figure 2), the similarity of results further strengthens the validity of the theoretical background of this analysis (Figure 1).

Our results provide one possible explanation why most RCTs in this field implemented their interventions for at least 2 months and up to a whole season, despite they lacked evidence of the dose–response relationship of their proposed EIPPs [2, 43, 47, 48]. Two meta-analyses examining strength training and neuromuscular training as injury prevention interventions found that only the EIPP's weekly volume, frequency, and intensity were associated with the preventive effect and not its overall duration [3, 43]. However, since all included studies except one had an intervention period of more than 10 weeks, we cannot extrapolate these findings for shorter periods of implementation. So, duration may still be associated with the preventive effect when looking at implementation periods shorter than 10 weeks. Furthermore, provided that structural adaptations at the tissue level are an important mediator of the preventive effect of EIPPs, our results agree with previous findings that the Nordic hamstring exercise increased the fascicle length and the pennation angle of the biceps femoris long head after 6 weeks of consistent training while some benefits could be seen after 2–3 weeks [32, 34, 49]. Similarly, the Achilles tendon stiffness, echo-intensity, and protein synthesis were found to be increased after 2 months of training, reaching a maximum after 3 months [31]. Overall, it appears that EIPPs need a certain time of regular practice to lead to adaptations that could mitigate injury risk. The amount of time necessary is both exercise- and goal-dependent, and being able to estimate it for a particular setting could have very important implications.

In our analysis, we identified and controlled for three possible effects that stemmed from the injuries sustained before the EIPP potentially developed its efficacy. Owing to this, we have shown that the original results from the PREVATHLE RCT were heavily impacted by these effects, which resulted in estimating a smaller, not-significant, effect than the one after controlling for them. Something similar could happen in other RCTs that do not differentiate between the EIPP implementation and the injury data collection periods. This could partially explain why a recent meta-analysis which used as inclusion criterion a simultaneous start of the intervention and injury data collection periods found no preventive effect of EIPPs for injury risk reduction in endurance runners, although several of the individual RCTs included showed an efficacy of their respective EIPP to reduce injury risk [36].

Regarding the specific effects what we controlled for, it seemed that the relative importance of the dilution effect in biasing the AIPP effect was much smaller than that of the reinjury and interaction effects. This can be seen by the minimal and non-significant change that was brought when controlling only for the dilution effect without controlling for the other two effects (Figures 2B and 3—red line). In contrast, the additional control of the reinjury (Figure 2D) and interaction effects (Figure 2C,E) brought larger and significant shifts on the estimated effect of the intervention (Figure 3). The relative importance of each effect could be different in other studies evaluating EIPPs. Which effect may have the largest or smallest contribution may be dependent on various factors, such as the EIPP's characteristics and its dose–response relationship, the population characteristics, and the outcome of interest. For example, the reinjury effect may be greater in cases where we are interested in one type of injury, while the dilution effect may have a greater impact in RCTs of EIPPs with longer periods until they become efficacious. Indeed, one of the two RCTs that considered separating the implementation from the analysis period, thus controlling just for the dilution effect, found that this consideration was enough to show a significant effect of the proposed EIPP, compared to the analysis including the implementation period which showed no effect [38].

4.1 | Strengths and Weaknesses

Two strengths of our analysis were (i) the exhaustive approach with regard to the length of the controlled period considered before the analysis period, which allowed for week-by-week analysis of the dose–response relationship, and (ii) the two approaches in the statistical analysis (stratification in the exclusion approach and inclusion of key control variables in the inclusion approach).

Regarding the limitations, in this secondary analysis it was not possible to provide confidence interval estimations for the temporal dimension of the dose–response relationship (i.e., when the increase and the peak in efficacy should be expected), as this would require multiple cohorts to be analyzed. Instead, we provided confidence intervals in the response dimension (i.e., how much effect could be expected after a given number of intervention implementation) which were specific to the AIPP and cannot be generalized for other EIPPs and populations. Second, it could be argued that there is high risk of type-I error, given the multiple analyses performed ($n = 120$). However, it could be counterargued that (i) each analysis was conducted on slightly different subsets of the whole dataset, (ii) we reported all results without "cherry-picking," in agreement with our preselected exhaustive approach, and more importantly, (iii) our results did not rely on absolute statistical significance but on the relative change of the observed effect with respect to the length of the controlled period considered. Thus, a type-I error may be possible but, in our case, irrelevant, meaning that even by adjusting the level of significance for multiple testing, this would not change the general pattern of the dose–response relationship. Lastly, there may be other effects interfering with the EIPP effect which we

did not control for in the analysis. These effects may explain the difference in the estimation of the EIPP effect between the exclusion and the inclusion approach after 12 weeks. This seems however not to impact significantly our results during the first weeks of implementation.

4.2 | Practical Implications

For researchers, this study shed light on the importance of acknowledging the dose–response relationship of an EIPP during the design and analysis of an RCT examining its efficacy. More concretely, we proposed two ways of analysis that can be used to estimate the dose–response relationship of EIPPs. This analysis could be supplemental to primary analyses of RCTs examining the effect of EIPPs on injury risk reduction, or it could be preliminary analyses of pilot studies aiming to explore the EIPP's dose–response relationship before finalizing the design and analysis protocols of RCTs. Given that these analyses changed remarkably the results of the RCT we examined, we invite researchers who have already conducted similar studies to reanalyze their results using these approaches and identify the dose–response relationships of their EIPP. Also, future research should examine whether the interaction effect of early-sustained injuries with the intervention is caused by biological or behavioral reasons. Moreover, additional analytical approaches could be employed to identify the period that an EIPP maintains its full efficacy. Finally, an integrated approach that combines this analysis with other factors contributing to EIPP's efficacy (e.g., program development, program implementation) would be ideal to optimize EIPP efficacy [8, 20–23].

For athletes, coaches, clinicians, and practitioners, this study provided evidence that an EIPP should be timely planned. If maximal effect is sought during a targeted period, such as a period of increased training load or frequent competitions, the EIPP should start well in advance before this period, according to the estimated EIPP dose–response relationship. Also, EIPP implementation should be planned during periods of minimal injury risk, such as early in the preparatory phase where there is less exposure. This could help in minimizing injuries during the early implementation period that could interact with the sought EIPP's adaptations, reducing the efficacy of the program. In general, we suggest that EIPPs should be integrated with all other training modalities during the sports season plan, and not considered as an adjunct to training.

5 | Perspectives

In the present study, we determined the dose–response relationship of an EIPP: the Athletics Injury Prevention Programme needed approximately 5–6 weeks before showing a significant injury risk reduction of approximately two-thirds. This information is essential for athletes, coaches, practitioners, and clinicians as it would help them determine the best implementation period of EIPPs. So, we suggest athletes, coaches, practitioners, and clinicians implement the AIPP 5–6 weeks before the targeted period where more protection is needed. On methodological and analytical perspectives, estimating the dose–response relationship of EIPPs is key to better estimate their isolated effect and should be considered when designing and analyzing studies that evaluate such programs.

Author Contributions

P.E. conceived the initial randomized controlled trial; S.I. conceived the secondary analysis; S.I., P.E., P.-E.D., D.B., and L.N. discussed the statistical plan and S.I. performed the statistical analyses; S.I. and P.E. wrote the first draft of the manuscript, and all co-authors contributed to the critical revision for important intellectual content and approval of the final manuscript. S.I. is the guarantor of the manuscript.

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Ethics Statement

This randomized controlled trial was reviewed and approved by the Committee for the protection of persons (CPP Ouest II—Angers, number: 2017-A01980-53).

Conflicts of Interest

The authors declare no conflicts of interest. P.E. is an Associate Editor for the *British Journal of Sports Medicine*, the *BMJ Open Sport & Exercise Medicine*, and the *Scandinavian Journal of Medicine & Science in Sports*.

Data Availability Statement

The data that support the findings of this study are available on request from the author Pascal Edouard (pascal.edouard@univ-st-etienne.fr). The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.