



# Metabolomics analyses and physical interventions in soccer: a systematic review

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## Abstract

**Background** Soccer is the most recognized sports worldwide. It is a fertile ground for the use of metabolomics analyses, considering the multifactorial nature of soccer's physical demands on the body. Although scientific studies have tried using it to better understand the impacts of soccer into different contexts of the sport, no systematic review is available on metabolomics analyses in soccer athletes subjected to physical exertion interventions.

**Aim of Review** Retrieve scientific articles that conducted metabolomics analyses on soccer athletes subjected to physical exertion interventions.

**Key Scientific Concepts of Review** Initially, 271 studies were screened, and 48 were retrieved for abstract analysis. Of these, 26 met the eligibility criteria, but 5 failed to meet inclusion criteria. The 21 studies included in this systematic review demonstrate that responses from physical training or acute exercise sessions, followed by the effects of soccer matches, have been the primary focus of researchers to date, highlighting alterations on metabolites from the energy metabolism, immunological pathway, purines, tryptophan/phenylalanine metabolism, as well as oxidative species and antioxidant capacity. Other studies suggest, albeit preliminarily, that organic metabolites have the potential to distinguish soccer players' performance and physical fitness, as well as provide valuable insights into diet, physical condition, training load, and recovery throughout the season. Despite metabolomics great potential to understand physiological alterations provoked by soccer as shown by the included studies, future studies should consider female athletes, explore the cause-and-effect relationship between metabolites and soccer performance more deeply, and examine the effects of different training periodizations on these markers.

**Keywords** Metabolomics · Mass spectrometry · Nuclear magnetic resonance · Metabolites · Physical training

## 1 Introduction

Soccer is played globally, generating significant revenue from national and international competitions (Coates et al., 2014; Scarfe et al., 2021; Solberg & Haugen, 2010). Due to its widespread recognition, it has been a topic of interest of several studies. For instance, systematic reviews with meta-analyses have successfully gathered studies aimed at understanding soccer related issues concerning injury prevention (Al Attar et al., 2016; Al Attar & Alshehri, 2019; Grimm et al., 2015), physiological stress induced by matches (Silva et al., 2018), nutrient intake (Mielgo-Ayuso et al., 2019; Steffl et al., 2019), dropout rates in youth athletes (Mollerlokken et al., 2015), or body composition of professional players (Sebastia-Rico et al., 2023).

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Among the scientific fields related to soccer, significant attention has been given to the use of serum molecules to assess fitness status (Manzi et al., 2022; Nobari et al., 2021; Perroni et al., 2020) and to analyze the effects of physical training (Clemente et al., 2021; McEwan et al., 2020). In this context, a systematic review indicated that long-term soccer training in male elite and professional players leads to variations in physical performance but also hematological, hormonal, inflammatory, and muscle damage markers (Saidi et al., 2021). A recent narrative review discussed biomarkers of post-match recovery in semi-professional and professional soccer (Perez-Castillo et al., 2023). Although this study demonstrated that several serum molecules can be used in the discussed context, the authors suggest that broad-spectrum analytical techniques, such as metabolomics, may provide additional insights. In fact, omics analyses focus on understanding metabolic alterations from a holistic perspective, which can be overlooked if the decision-making process during exercise prescription is based on some few specific biomarkers.

Metabolomics is the comprehensive and quantitative analysis of all metabolites found within cells, biofluids, tissues, or entire organisms (Fiehn, 2001). Together, these metabolites and their interactions within a biological system make up what is known as the metabolome (Tweeddale et al., 1998). The newest member of the “omics” family has opened new horizons for studies related to sports, with the term “sportomics” even being adopted in scientific research (Bassini et al., 2022; Bragazzi et al., 2020; Goncalves et al., 2022). Mass spectrometry (MS), nuclear magnetic resonance (NMR), and other high throughput screening techniques are used to detect and quantify metabolites in two different approaches, the untargeted and the targeted one (Lee & Banerjee, 2020). The untargeted approach uses an unbiased screening method to identify thousands of metabolites in a single experiment, and thus enables exploratory studies of unknown metabolites and hypothesis generation. Conversely, the targeted approach aims at detecting specific molecules of interest in a biological pathway, and is used to confirm or validate a previous hypothesis (Amer et al., 2023; Chen et al., 2020; Lelli et al., 2021; Zullig et al., 2020). Through these techniques, it is possible to identify a wide range of metabolites using easily accessible biological matrices, such as urine, sweat, saliva, or blood (Denery et al., 2011; Dettmer et al., 2007; Ren et al., 2018). Given the use of biomarkers in studies exploring various aspects of soccer, it is not surprising that researchers have employed metabolomics to investigate soccer-related fields. Studies ranging from the analysis of dietary supplement intake (Al-Khelaifi et al., 2018), to the association of the metabolome with leucocyte telomere length (Al-Muraikhy et al., 2021) in soccer players can be found in the specialized literature.

Within the realm of soccer metabolomics, researchers have dedicated efforts to understanding the effects that physical exertion in soccer—whether through physical tests, training, or matches—has on the metabolome of players. As a matter of fact, acute and chronic structured exercise has the potential to provoke a myriad of biological adaptations on the body (Davies et al., 2021; Edwards et al., 2023; Jukic et al., 2021; Lock et al., 2024; Marshall et al., 2021), but the understanding of those must come through the gathering and analysis of the specialized literature, which has not been performed yet. Therefore, this systematic review aimed to retrieve scientific articles that conducted metabolomics analyses on soccer athletes subjected to physical exertion interventions.

## 2 Methods

### 2.1 Search strategy

The search strategy was devised and conducted by a researcher experienced in systematic reviews and meta-analyses. Until April 3, 2024, Web of Science, PubMed, and Scopus databases were queried without restrictions on published data. Boolean operators such as “AND,” and “OR,” were employed with specific filters for each database. In WOS and PubMed, the combinations were (soccer OR football) AND (metabolomics OR metabolites OR lipidomics OR metabolic profile), with the “Humans” filter considered. Regarding Scopus, the structure (soccer OR football) AND (metabolomics OR metabolites OR lipidomics OR metabolic profile) AND (LIMIT-TO (DOCTYPE, “ar”)) AND (LIMIT-TO (LANGUAGE, “English”)) AND (LIMIT-TO (EXACTKEYWORD, “Human”)) was used. In addition to the searches in the databases, the reference lists of the considered articles were checked. The databases, along with the terms used, were re-evaluated on September 10, 2024.

### 2.2 Eligibility criteria and inclusion/exclusion criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) was used to screen the potential studies. This process was conducted in three stages, considering title, abstract, and full text. Discrepancies were reviewed at each stage, and consensus was reached in all cases. Table 1 presents the PICOS criteria (Methley et al., 2014), which guided eligibility analysis. For meticulous inclusion, studies were considered if: (a) conducted metabolomic analyses in soccer, regardless of the situation, athletes’ level, or gender; (b) clearly outlined all necessary steps for metabolite analysis, including sample

**Table 1** The population, intervention, comparator, outcomes, and study design (PICOS) components adopted for eligibility criteria of studies in this systematic review

Components	Features
(P) Population	Soccer athletes regardless of the level or non-athletes
(I) Intervention	Physical interventions conducted with soccer players, such as acute sessions, physical training, or physiological testing
(C) Comparator	Within or between subjects, considering cross-sectional or longitudinal analyses
(O) Outcomes	Metabolites
(S) Study Design	Brief reports, case-control, or randomized controlled trials.

acquisition and extraction, as well as all procedures and techniques for metabolomics; (c) presented specific results for the soccer group when the study included athletes other than soccer players; (d) employed experimental designs where the only intervention applied was soccer, excluding other factors such as psychological aspects, nutrition, medication use, or ergogenic aids, for instance. However, if a study presented an isolated group for any of these interventions, it was included; (e) that detailed all bioinformatics procedures for metabolomics data analysis. On the other hand, studies were excluded if: (a) only the abstract was provided; (b) only sample characterization was presented, without necessarily showing the effects of a specific training session, match, competition, or season on the metabolome; (c) in cases where contact with the authors for clarification yielded no response.

### 2.3 Data extraction

An experienced author in systematic reviews (LHDM) searched the databases. The titles of the articles were entered into Microsoft Excel spreadsheets and sent separately to the reviewers. Three authors (LCP, JPC, and GCB) independently screened the manuscripts. Following the retrieval of articles, independent spreadsheets were created and forwarded to the authors. In case of discrepancies, a fourth reviewer (LHDM) was consulted. All discrepancies were resolved through consensus. The extracted data encompassed: (a) characteristics of the sample, including anthropometrics, body composition, and age; (b) level of athletes (amateur or professional); (c) physiological matrices like blood (total, serum, plasma, or cells), tissue, saliva, urine, or feces; (d) method and equipment used for metabolomics; (e) condition used in the study (e.g. rest, before or after games); and key findings.

## 2.4 Quality assessment

A risk-of-bias form adapted to soccer from Sarmiento et al. (2018) was considered for quality assessment of the included studies. The checklist consists of 16 items, including (1) purpose; (2) relevance of background literature; (3) appropriateness of study design; (4 and 5) sample studied; (6) use of informed consent procedure; (7 and 8) outcome measures; (9) method description; (10) significance of results; (11) analysis; (12) practical importance; (13) description of dropouts; (14) conclusions; (15) practical implications; (16) limitations. Every question received a binary score of 0 (indicating “no”) or 1 (indicating “yes”), except questions 6 and 13, which allowed for an additional option: “If not applicable, assume 3.” The total score was calculated by summing all responses, then divided by the maximum possible score for a study (i.e., 16) and expressed as a percentage. Based on these percentages, the included studies could be classified into three categories: (a)  $\leq 50$  = low methodological quality; (b) between 51 and 75% = good methodological quality lies; (c)  $> 75\%$  = excellent methodological. Two researchers performed the quality assessment (PPMS and LHDM) and any discrepancies were resolved through discussion. The bias plot was created using the Robvis Tool (Risk-of-Bias-Tool, 2024).

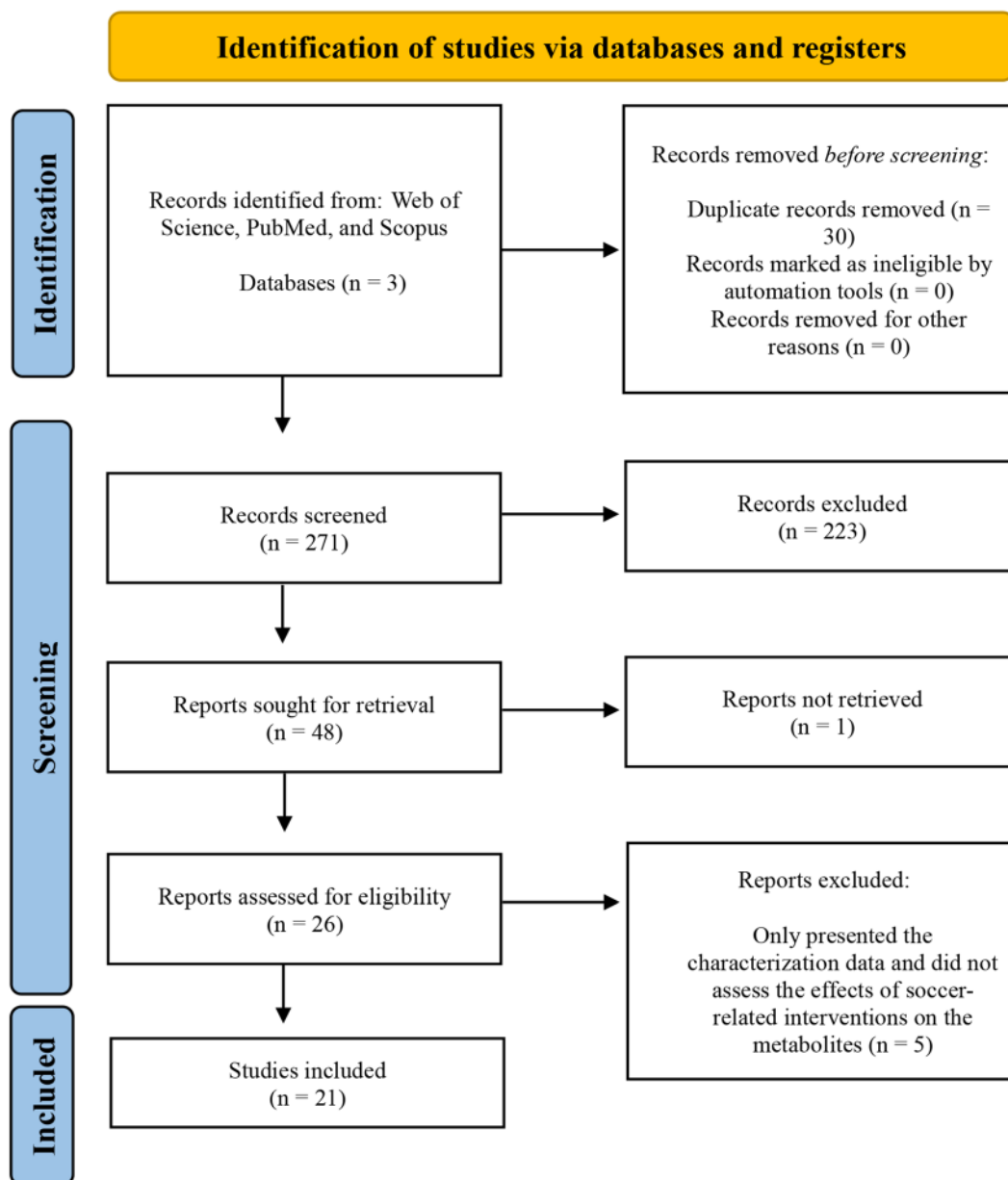
## 3 Results

### 3.1 Included studies and quality assessment

Figure 1 displays the PRISMA chart, showing all processes related to screening. After the title screening, 223 studies were excluded from further abstract and full-text analysis. At the end of this stage, twenty-one studies met the eligibility criteria. The eligible studies were published between 2014 and 2024 (Alzahrani et al., 2019; Alzharani et al., 2020; Cao et al., 2020; Cruz et al., 2022; Franca et al., 2023; Gonzalez et al., 2024; Gouveia et al., 2024; Kim et al., 2022; Ksiazek et al., 2023; Luti et al., 2022; Marinho et al., 2022; Nunes et al., 2021; Peña et al., 2023; Pintus et al., 2021; Pitti et al., 2019; Prado et al., 2017; Quintas et al., 2020; Ra et al., 2014; Rodas et al., 2022; Santone et al., 2014; Zhao et al., 2020). Two studies were classified with good methodological quality (Kim et al., 2022; Zhao et al., 2020), while the remaining studies were classified as excellent (Supplementary File 1).

### 3.2 Characteristics of the samples

A total of 637 individuals underwent soccer-related interventions and metabolite analysis. Only one study did not



**Fig. 1** The preferred reporting items for systematic reviews and meta-analyses (PRISMA) used to screen the potential studies

report the sex of the athletes ( $n=23$ ). Among the remaining studies, 491 were men (sixteen studies) and 123 were women (five studies). One study included men and women in the sample set (Rodas et al., 2022). Regarding the athletes' level, 71% of the included studies focused on professional athletes, while 29% examined young athletes (elementary or high school) or non-professional athletes.

### 3.3 Physiological matrices, analytical method, and targets

Urine was the most commonly used physiological matrix among the included studies (twelve studies), followed by

saliva (five studies). One study that used urine as a biological matrix reported the average water intake of the athletes ( $2.9 \pm 0.8 \text{ L} \cdot \text{d}^{-1}$ ) as well as baseline urine color, adopting a scale ranging from 1 to 8 ( $2.7 \pm 0.9$ ), with color ranges from very pale yellow to brownish green (Marinho et al., 2022). Four studies used either serum or plasma (two studies each), while sweat, and erythrocytes were each used in a single study. One report utilized plasma, urine, and saliva (Alzharani et al., 2020). Untargeted analysis was used in 76% of the eligible studies (sixteen studies), while 24% employed targets for specific metabolites (five studies). The targets included testosterone, dehydroepiandrosterone, and epitestosterone (Alzahrani et al., 2019), tryptophan and

phenylalanine pathways and amino acids (Gonzalez et al., 2024; Rodas et al., 2022), total and free Vitamin D and its metabolite levels (Ksiazek et al., 2023) and polyunsaturated fatty acids (Peña et al., 2023). Regarding the analytical methods, Nuclear Magnetic Resonance was used in six studies (29%). Liquid Chromatography was used in eleven studies (52%), while, Capillary Electrophoresis Time-of-Flight and Gas Chromatography were considered in one (5%) and three (14%) studies, respectively.

### 3.4 Conducted interventions

Most of the eligible studies compared organic metabolites at different times during the season (38%, eight studies) (Table 2), while six reports examined the effects of simulated or official matches (29%) (Table 3). Five studies focused on the analysis of organic metabolites concerning physical training (24%) (Table 4), and the remaining two studies (9%) used physical tests for metabolome analysis (Table 5), either to assess the stressor effect of the test or to classify the athletes' level based on the physiological assessment results in conjunction with the metabolites.

Regarding physical training interventions, four studies considered acute sessions (one or two sessions) (Alzahrani et al., 2019; Alzahrani et al., 2020; Cao et al., 2020; Zhao et al., 2020), while one study focused on chronic physical training without specifying the total duration (Luti et al., 2022). Two studies employed two small-sided games for 30 min, followed by a 4-minute rest, and then a 40-minute game divided into two halves, with an approximate intensity of 70–72% of maximum heart rate (Alzahrani et al., 2019; Alzahrani et al., 2020). One study used the Yo-Yo intermittent recovery test as a model for high-intensity interval training (Zhao et al., 2020), while another study adopted a training protocol combining aerobic and anaerobic efforts on a cycle ergometer (Cao et al., 2020). In the latter, the exercise model involved aerobic exercise followed by 1 min of rest, then anaerobic exercise with a 3-minute rest, repeated performed in a total of three training times. For the aerobic effort, a cadence of 55–60 rpm generating 150 W of power was used. The last study involved continuous training, conducted five times per week and 2 h per day, with the protocol comprising technical, aerobic, and strength exercises (Luti et al., 2022). Specifically for strength training, volumes of 3 sets of 12–15 repetitions were utilized. Detailed descriptions of the intensity levels used for technical, aerobic, or strength efforts were not provided.

## 4 Discussion

This study presents the first systematic review regarding metabolomic analyses of soccer athletes subjected to physical exertion interventions. Responses from physical training or acute exercise sessions, followed by the effects of soccer matches, have been the main focus of researchers to date. Although this systematic review retrieved a significant number of studies within the realm of soccer-metabolomics, several gaps in this context remain. Limited information is available on the modulation of organic metabolites throughout the soccer season, as well as the relationship between responses from physical tests and the metabolome of these athletes. Equally important, this review highlights the need for more studies involving female soccer athletes.

A myriad of interventions on metabolomic responses was observed in the eligible studies. Although Alzahrani et al. (2019) study focused on sample preparation for the target's testosterone, dehydroepiandrosterone, and epitestosterone, the authors also investigated the effects of two acute training sessions (small-sided games and a match) on these markers. While serum testosterone remained unchanged during these sessions, significant increases in dehydroepiandrosterone were observed. The authors attribute this increase to the nature of the effort required of soccer players, specifically brief and intense exercises. However, detailed explanations regarding how soccer training specifically influenced this marker is lacking. These results are partially distinct when compared to the study by Zhao et al. (2020), where testosterone, along with other steroid hormones, amino acid biosynthesis metabolites, and protein expression, were modulated by a session of high-intensity interval training. Such results were attributed to the oxidative stress triggered by effort. Further, the fact that steroid hormones were downregulated post-exercise and upregulated during recovery possibly indicates enhanced muscle growth following high-intensity interval training sessions. However, it is important to point the differences between the studies, as they analyzed different matrices (saliva vs. urine), using different analytical approaches (target vs. untarget), and after different physical exertion. Despite the discrepancies, these studies reinforce that metabolomics can detect hormonal changes in soccer athletes, which are regularly discussed in the specialized literature (Koundourakis & Margioris, 2019; Slimani et al., 2017; Strahm et al., 2009).

Discussions related to energy metabolism or other types of metabolic changes in soccer are regularly revisited in the literature (Hulton et al., 2022; Koundourakis & Margioris, 2019; Randell et al., 2021; Slimani et al., 2017; Strahm et al., 2009). The studies included in this systematic review support the hypothesis that metabolomics can identify not only modulations in energy metabolism but also reveal metabolic



**Table 2** Key characteristics of the included studies examining metabolites fluctuation along the season

Study	Sample	Physiological Matrice	Analytical approach and targets	Condition (C) and key findings (KF)
Pintus et al., 2021	<i>N</i> = 21 <b>Sex</b> = male <b>Level</b> = professional <b>Age</b> = 25 ± 4 yrs	Urine	- <sup>1</sup> H-NMR at 300 K on a Varian Unity Inova 500 MHz (Agilent); - Untarget analysis	<b>C</b> – Urine metabolites were compared among three time points during the pre-season, in which T1, T2, and T3 correspond to the 2nd, 6th, and 16th day of training session; <b>KF</b> – T1 showed high levels of trimethylamine oxide. T2 and T3 showed higher amounts of creatine, hippuric acid, and guanidoacetic acid. T2 was found to be richer in 3-hydroxybutyrate, citrate, and hippurate. T3 showed higher levels of hypoxanthine, guanidoacetic acid, citrate, and hippurate. These metabolites were associated with diet, training, and microbiota.
Quintas et al., 2020	<i>N</i> = 80 <b>Sex</b> = male <b>Level</b> = professional <b>Age</b> = 16–21 yrs	Urine	- UHPLC-QTOF-MS on an Agilent 6550; - ESI(+); - Full Scan ( <i>m/z</i> 100–1700); - Untarget analysis.	<b>C</b> – Urine metabolites were assessed among five time points, in which T1 refers to preseason and T2, T3, T4, and T5 after 3, 5, 8, and 10 months of competition, and associated with external load of training; <b>KF</b> – steroid hormone metabolites, hypoxanthine metabolites, acetylated amino acids, intermediates in phenylalanine metabolism, tyrosine, tryptophan metabolites, and riboflavin among the most relevant variables associated with external load.
Kim et al., 2022	<i>N</i> = 14 <b>Sex</b> = male <b>Level</b> = young players <b>Age</b> = 10–13 yrs	Urine	- <sup>1</sup> H-NMR acquisition on a Varian Unity Inova 600 MHz; - Untarget analysis.	<b>C</b> – Urine metabolites were analyzed after 1, 5 and 10 days of the winter training season and tested as potential markers for recovery times; <b>KF</b> – 15 metabolites, including 1-methylnicotinamide, 3-indoxylsulfate, galactarate, glutamate, glycerol, histamine, methylmalonate, maltose, N phenylacetyl glycine, trimethylamine, urea, 2-hydroxybutyrate, adenine, alanine, and lactate, were significantly modified by the training. Most selected metabolites increased 1 day after the training and then returned to regular level, while adenine, 2-hydroxybutyrate, alanine, and lactate increased during the five days of recovery.
Rodas et al., 2022	<i>N</i> = 51 <b>Sex</b> = female (28) and male (23) <b>Level</b> = professional <b>Age</b> = female – 25 ± 5 yrs; male – 25 ± 5 yrs	Urine	- UHPLC-MS/MS on a triple quadrupole (Agilent 6460); - ESI(+); -MRM; - Target (tryptophan and phenylalanine pathways and amino acids).	<b>C</b> – Urine metabolites were associated with external load to verify athletes' adaptation to the training; <b>KF</b> – aminoacids, tryptophan and phenylalanine metabolites detected progressive changes associated with the external training load.
Ksi-azek et al., 2023	<i>N</i> = 20 <b>Sex</b> = male <b>Level</b> = professional <b>Age</b> = 26 ± 4 yrs	Serum	- UHPLC-MS/MS on a triple quadrupole (5500 QTRAP AbSciex); - ESI(+); - MRM; - Target (total and free Vitamin D and its metabolite levels)	<b>C</b> – Serum total and free Vitamin D and its metabolite levels were assessed at six different time points over half a year. In addition to examining the correlation of total and free Vitamin D and its metabolites with psychophysical stress markers, they were also compared throughout the season to determine whether variations in training load affected the vitamin D metabolome. <b>KF</b> – A seasonal pattern was observed for total vitamin D and its metabolites, though not for free vitamin D. Correlations between free and total vitamin D levels and psychophysical stress markers did not indicate that free measurements were more informative than total ones. Finally, varying training loads across different training phases had no impact on resting concentrations of vitamin D metabolites in soccer players.
Peña et al., 2023	<i>N</i> = 40 <b>Sex</b> = female <b>Level</b> = professional <b>Age</b> = 24.4–24.5 yrs <sup>§</sup>	Erythrocyte membranes	- GC-FID acquisition on an Agilent 6850 Network GC System - Target (fatty acid families - saturated, monounsaturated, and polyunsaturated fatty acids)	<b>C</b> – The lipid profile of mature erythrocyte membranes was compared across three consecutive seasons (2019–2020, 2020–2021, and 2021–2022). <b>KF</b> – While docosahexaenoic acid increased in the first season, membrane arachidonic acid rose in the second. Total polyunsaturated fatty acids increased in both seasons 1 and 2.

**Table 2** (continued)

Study	Sample	Physiological Matrice	Analytical approach and targets	Condition (C) and key findings (KF)
Gonzalez et al., 2024	<i>N</i> = 24 <b>Sex</b> = female <b>Level</b> = professional <b>Age</b> = 17–31 yrs	Urine	- UHPLC-MS/MS on a triple quadrupole (Agilent 6460); - ESI(+); -MRM; - Target (tryptophan and phenylalanine pathways and amino acids). - <sup>1</sup> H-NMR - acquisition at 300 K on a Bruker 600 MHz Avance III; - Untarget analysis.	<b>C</b> – Of the 24 athletes included in the sample, 19 were tested at 4 time points over two seasons, aiming to associate urinary metabolites with injury risk. <b>KF</b> – While Beta-alanine was inversely associated with injury risk, serotonin and 5-hydroxy-tryptophan were directly associated with injury risk. Further, the prediction of injury risk was more effective when integrating omics technologies with external workload assessments, compared to relying solely on external workload data.
Gouveia et al., 2024	<i>N</i> = 14 <b>Sex</b> = female <b>Level</b> = professional <b>Age</b> = 19–32 yrs	Urine	- <sup>1</sup> H-NMR - acquisition at 300 K on a Bruker 600 MHz Avance III; - Untarget analysis.	<b>C</b> – Urine metabolites were compared in three pre-and post-game moments during a championship season; <b>KF</b> – As the championship season progressed, the metabolites present in urine (glycine, formate, citrate, 3-hydroxyvalerate, glycolic acid, trimethylamine, urea, and dimethylglycine) increased the separation between time points, representing energy and protein metabolism. These changes may be associated with the accumulation of fatigue.

<sup>1</sup>H-NMR - Proton Nuclear Magnetic Resonance; UHPLC-QTOF-MS - Ultra-High Performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry; UHPLC-MS/MS - Ultra-High Performance Liquid Chromatography-Tandem Mass Spectrometry; MRM - Multiple Reaction Monitoring; ESI - Electrospray Ionization; GC-FID - Gas Chromatography with Flame Ionization Detector; §median values were considered at the first and last time points monitored

responses that still require further exploration regarding their impact on soccer players. Cao et al. (2020) employed a protocol combining aerobic and anaerobic efforts to explore which metabolic pathways might be involved in this dynamic. The authors observed that protein metabolism, tricarboxylic acid cycle metabolism, and lipid metabolism were engaged during these efforts in teenage soccer players, suggesting this approach as a model to induce a state of body fatigue in this population. After subjecting professional soccer players to short-term high-intensity efforts, Alzharani et al. (2020) observed a significant post-exercise increase in acylcarnitines, suggesting that these well-trained athletes rely more on fat than glucose as an energy source. Not less importantly, metabolomics was able to distinguish responses in oxidative species, antioxidant capacity, and adiponectin levels, when comparing training programs between basketball and soccer players (Luti et al., 2022). This result is particularly interesting as suggests that metabolomics is able to identify metabolic responses specific to the training imposed by these sports.

Another condition highlighted by this study lies in the interest in understanding the metabolic modulations resulting from soccer matches. Although most of the eligible studies observed changes in energy metabolism, distinct metabolites were also identified. Ra et al. (2014) observed that three consecutive days of soccer matches led to increases in 3-methylhistidine, glucose 1- and 6-phosphate, taurine, and certain amino acids, which are linked to energy metabolism and may serve as fatigue markers in male intercollegiate athletes. However, eligible studies indicate that a single match can already modulate the metabolome in soccer athletes. Prado et al. (2017) suggests that the rise in hypoxanthine and related metabolites following a match with

semi-professional male players points to increased adenosine monophosphate deamination, with the rise in adenosine triphosphate utilization implying adenosine diphosphate resynthesis via myokinase. For professional female athletes, Pitti et al. (2019) provides two key insights following a soccer match. The study revealed that the goalkeeper displayed unique metabolic variations, suggesting that saliva biomarkers were sensitive to both the specific activity and the player's position. Furthermore, the changes in metabolite levels were not consistent, indicating a reduction in water content and varied physiological responses induced by the exercise. Subsequently, 26 potential biomarkers associated with the stress generated by a match were identified in non-professional male athletes (Nunes et al., 2021). In addition to observing metabolites related to energy production, cellular damage, and organic stresses immediately after a soccer match, and antioxidant and anti-inflammatory pathways 20 h post-match, Marinho et al. (2022) also suggests the use of the subjective effort perception scale to differentiate metabolites after a match in male professional athletes. Considering a context distinct from the studies presented thus far, Franca et al. (2023) suggests that the metabolic changes observed immediately after a soccer match indicate that this effort could serve as a potential model to search for countermeasures in Hawkinsinuria and other tyrosine metabolism disorders.

The differences observed in these reports are impacted by the choice of the physiological matrix, the analytical approach, and the particular characteristics of each game. Each biological matrix requires a specific extraction method during metabolomic analyses; equally important, different metabolites can be identified depending on the analytical approach and bioinformatics (Beger et al., 2024; Chetwynd

**Table 3** Key characteristics of the included studies involving the effects of simulated or official matches

Study	Sample	Physiological Matrice	Analytical approach and targets	Condition (C) and key findings (KF)
Ra et al., 2014	N = 122 Sex = male Level = college Age = 20 ± 0 yrs	Saliva	- CE-TOF-MS performed using an Agilent CE (capillary electrophoresis); - ESI(-); - Full Scan ( <i>m/z</i> 50–1000); - Untarget analysis.	C – Salivary fatigue markers were assessed in soccer players before and after a sequence of 3 games played in consecutive days, one per day, as part of a game program; KF – A significant metabolomic difference was observed before and after the program, including 3-methylhistidine, glucose 1- and 6-phosphate, taurine, and some amino acids.
Prado et al., 2017	N = 30 Sex = male Level = semi-professional Age = 18–20 yrs	Urine	- UHPLC-TOF-MS <sup>E</sup> on a Xevo-G2XS QTOF (Waters); - ESI(+); - DIA ( <i>m/z</i> 50-1000); - Untarget analysis.	C – Urine metabolomics was assessed before and after a soccer match to investigate metabolic alterations in response to acute intermittent exercise; KF – Hypoxanthine and related metabolites were up-regulated in urine after a soccer match, suggesting that AMP deamination was increased. The overall data collected also suggest that during a soccer game, there was an increase in ATP use provided by ADP synthesis via myokinase.
Pitti et al., 2019	N = 17 Sex = female Level = professional Age = 23 ± 5 yrs	Saliva	- <sup>1</sup> H-NMR; - acquisition at 298 K on a Bruker 600 MHz Avance; - Untarget analysis.	C – Salivary metabolite samples were compared before and after an official match; KF – Metabolites associated with energy, hydration status, amino acids, and other compounds were different between before and after time points.
Nunes et al., 2021	N = 10 Sex = male Level = healthy volunteers Age = 22–26 yrs	Sweat	- UHPLC-MS/MS on a triple-quadrupole (TSQ Quantis, Thermo); - ESI(+/-); - MRM; - Untarget analysis.	C – Sweat metabolites were tested as potential stress biomarkers after an intense training game; KF – 26 potential biomarkers were identified, including monoamines, amino acids and precursors of biogenic amines, acetylcholine, adenosine, carboxylic acids, carbohydrates, breakdown products, and steroid hormones. Of the molecules identified, stress-related biomarkers were found, such as epinephrine or cortisol.
Marinho et al., 2022	N = 23 Sex = male Level = professional Age = 19 ± 1 yrs	Urine	- <sup>1</sup> H-NMR; - acquisition at 300 K on a Bruker 600 MHz Avance III; - Untarget analysis.	C – Urine metabolites along with the rating of perceived exertion scale were adopted to discriminate metabolites immediately and 20 h after soccer matches; KF – Metabolites associated with energy production, cellular damage, and organic stresses were changed immediately after the game. 20 h after the games, anti-oxidant and anti-inflammatory pathways related to cell recovery were identified. Soccer athletes with higher rating of perceived exertion values showed a high metabolite profile related to muscle damage (e.g., creatine, creatinine, and glycine) and energy production (e.g., creatine, formate, pyruvate, 1,3 dihydroxyacetone) 20 h post-soccer match.
Franca et al. (2023)	N = 30 Sex = male Level = Junior Age = 19.2 ± 0.2 yrs	Urine	- UHPLC-TOF-MS <sup>E</sup> on a Xevo-G2XS QTOF (Waters); - ESI(+); - DIA ( <i>m/z</i> 50-1000); - Untarget analysis.	C – Urine metabolites were used to assess changes in metabolism during a soccer match; KF – The match caused a downregulation (4-maleylacetoacetate and succinylacetone to 20% and 16%, respectively), while 4-Hydroxyphenylpyruvate, was found to be upregulated by 26%. The concentration of hawkinsin and its metabolite 4-hydroxycyclohexyl acetate increased six-fold. DOPA and dopaquinone increased four to six-fold. 3-Methoxytyrosine, indole-5,6-quinone, and melanin were downregulated from 1 to 25%, as were dopamine and tyramine.

**CE-TOF-MS** - Capillary Electrophoresis Time-of-Flight Mass Spectrometry; **ESI** - Electrospray Ionization; **UHPLC-TOF-MS<sup>E</sup>** - Ultra-High Performance Liquid Chromatography-Time-of-Flight Mass Spectrometry with Elevated Energy; **DIA** - Data-Independent Acquisition; **<sup>1</sup>H-NMR** - Proton Nuclear Magnetic Resonance; **UHPLC-MS/MS** - Ultra-High Performance Liquid Chromatography-Tandem Mass Spectrometry; **MRM** - Multiple Reaction Monitoring

et al., 2017; Garwolinska et al., 2023; Gonzalez-Dominguez et al., 2020; Lee & Kim, 2017; Schneider & Orchard, 2011; Wu & Li, 2016). Equally important, a myriad of factors like physical, environmental, tactical, situational, or players position may impact the soccer match (Forcher et al., 2023; Harkness-Armstrong et al., 2022; Sarmiento et al., 2014; Trewin et al., 2017). All studies used only a few games

(up to three) to characterize the impact of the match on the metabolic profile, and future studies may need to involve more games with a similar biological matrix to investigate the extent of these contextual factors may had on the results perceived by metabolomics. In this context, the literature still lacks studies that provide robust characterizations of the match to contrast with the modulated metabolites.



**Table 4** Key characteristics of the included studies focused on physical training

Study	Sample	Physiological Matrice	Analytical approach and targets	Condition (C) and key findings (KF)
Alzahrani et al., 2019	<i>N</i> = 20 Sex = male Level = professional Age = 20.6 ± 1.4 yrs	Saliva	- HPLC-MS/MS on a triple quadrupole (G6430A, Agilent); - ESI(+); - MRM; - Target (testosterone, dehydroepiandrosterone, and epitestosterone).	<b>C</b> – Testosterone, dehydroepiandrosterone, and epitestosterone assessed in saliva were compared before and after two exercise sessions; <b>KF</b> – The saliva testosterone was not different before and after training, while dehydroepiandrosterone increased significantly.
Cao et al., 2020	<i>N</i> = 12 Sex = male Level = high school Age = 14–16 yrs	Urine	- GC-TOF-MS on an Agilent 7890; - Electron Ionization; - Full Scan ( <i>m/z</i> 50–500); - Untarget analysis.	<b>C</b> – Urine metabolites were compared before and after combined exercise session in a cycle ergometer aiming to understand the metabolic mechanism underlying exercise-induced fatigue; <b>KF</b> – 25 different metabolites were different between time points, which belong to glycine-serine-threonine metabolism, citrate cycle, tyrosine metabolism, nitrogen metabolism, and glycerophospholipid metabolism.
Zhao et al., 2020	<i>N</i> = 23 Sex = Not provided Level = professional Age = 17 ± 2 yrs	Urine	- UHLC-QTOF-MS on a Triple TOF 6600 (Sciex); - ESI(+/-); - Full Scan ( <i>m/z</i> 100–1200); - Untarget analysis.	<b>C</b> – Urine metabolites were compared before and after high-intensity interval training; <b>KF</b> – Steroid hormone and amino acid biosynthesis metabolites were revealed by metabolomics as a function of the intervention, while proteomics showed changes in protein expression in metabolic pathways involved in energy metabolism, oxidative stress as well as immune pathways.
Alzahrani et al., 2020	<i>N</i> = 26 Sex = male Level = professional Age = 20 ± 1 yrs	Plasma, urine, and saliva	- HPLC-MS on a Exactive Orbitrap (ThermoFisher); - ESI(+/-); - Full Scan ( <i>m/z</i> 75–1200); - Untarget analysis.	<b>C</b> – Metabolites were compared before and after two exercise sessions; <b>KF</b> – A significant increase in acylcarnitines and a slight increase in purine metabolites were observed after the exercise sessions.
Luti et al., 2022	<i>N</i> = 30 (10 soccer, 10 basketball, and 10 controls) Sex = male Level = professional Age = soccer-20 ± 1 yrs; basketball-21 ± 2 yrs; controls-26 ± 4 yrs	Plasma	- GC-MS on a mono quadrupole (Agilent); - EI (+); - Full scan ( <i>m/z</i> 50–600); - Untarget analysis.	<b>C</b> – Plasma metabolites and redox homeostasis were assessed in basketball and soccer players, and potential metabolic pathways underlying the differences in training programs were verified; <b>KF</b> – Low levels of oxidative species (25.5%), with both high antioxidant capacity (17.6%) and adiponectin level (64.4%) in plasma were obtained from basketball players when compared to soccer players

**HPLC-MS/MS** - High Performance Liquid Chromatography coupled with Tandem Mass Spectrometry; **ESI** - Electrospray Ionization; **MRM** - Multiple Reaction Monitoring; **GC-TOF-MS** - Gas Chromatography-Time-of-Flight Mass Spectrometry; **UHLC-QTOF-MS** - Ultra-High Performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry; **HPLC-MS** - High Performance Liquid Chromatography-Mass Spectrometry; **UHPLC-MS/MS** - Ultra-High Performance Liquid Chromatography-Tandem Mass Spectrometry; **FIA-MS/MS** - Flow Injection Analysis coupled with Tandem Mass Spectrometry; **GC-MS** - Gas Chromatography-Mass Spectrometry

The remaining conditions in the eligible studies involve physical tests or metabolite analysis throughout the season. The Yo-Yo test, as well as its adaptations, is widely used to assess the aerobic fitness of soccer players (Deprez et al., 2012, 2014, 2015; Ingebrigtsen et al., 2012; Karakoc et al., 2012; Krstrup et al., 2006; Oberacker et al., 2012; Rampinini et al., 2010). The eligible study demonstrated that salivary metabolites responded to the physical stress caused by the Yo-Yo test (Santone et al., 2014). Additionally, these

authors clustered athletes into the arbitrary categories of Bad, Normal, and Good performers. Normal Performers were those who ran distances within one standard deviation around the mean ( $\pm 1/2$  standard deviations). In contrast, Bad Performers ran less than 154 m, while Good Performers exceeded 1921 m. Based on Principal Component Analysis, 20 metabolites were identified, highlighting creatine, lysine, leucine, choline, inositol, tyrosine, and glutamine. These metabolites were particularly significant in Component 1,

**Table 5** Key characteristics of the included studies using physical fitness tests

Study	Sample	Physiological Matrice	Analytical approach and targets	Condition (C) and key findings (KF)
San-tone et al., 2014	<i>N</i> = 14 Sex = male Level = elite professional Age = 23 ± 3 yrs	Saliva	- <sup>1</sup> H-NMR; - acquisition at 298 K on a Bruker Ultra-Shield spectrometer Avance700; - Untarget analysis.	<b>C</b> - Salivary metabolites were assessed before and after the level 1 Yo-Yo intermittent recovery test; <b>KF</b> - Salivary metabolites were sensitive to the induced physical stress by the Yo-Yo test and also allowed to cluster the best and the worst performing athletes.
Cruz et al., 2022	<i>N</i> = 36 Sex = male Level = professional (non-elite, <i>n</i> = 20; elite, <i>n</i> = 16) Age = non-elite-20 ± 2 yrs; elite-18 ± 1 yrs	Serum	- UHPLC-MS on a Orbitrap Q Exactive (Thermo); - ESI (+/-); - Full Scan ( <i>m/z</i> 100–1500); - Untarget analysis.	<b>C</b> - Serum metabolites were adopted to compare soccer players from distinct competitive levels; <b>KF</b> - 76 metabolites showed different relative abundances between groups. Elite soccer players presented increased metabolites belonging to the glycerolipid, lipid sterol, fatty acyl, flavonoid, and glycerophospholipid classes.

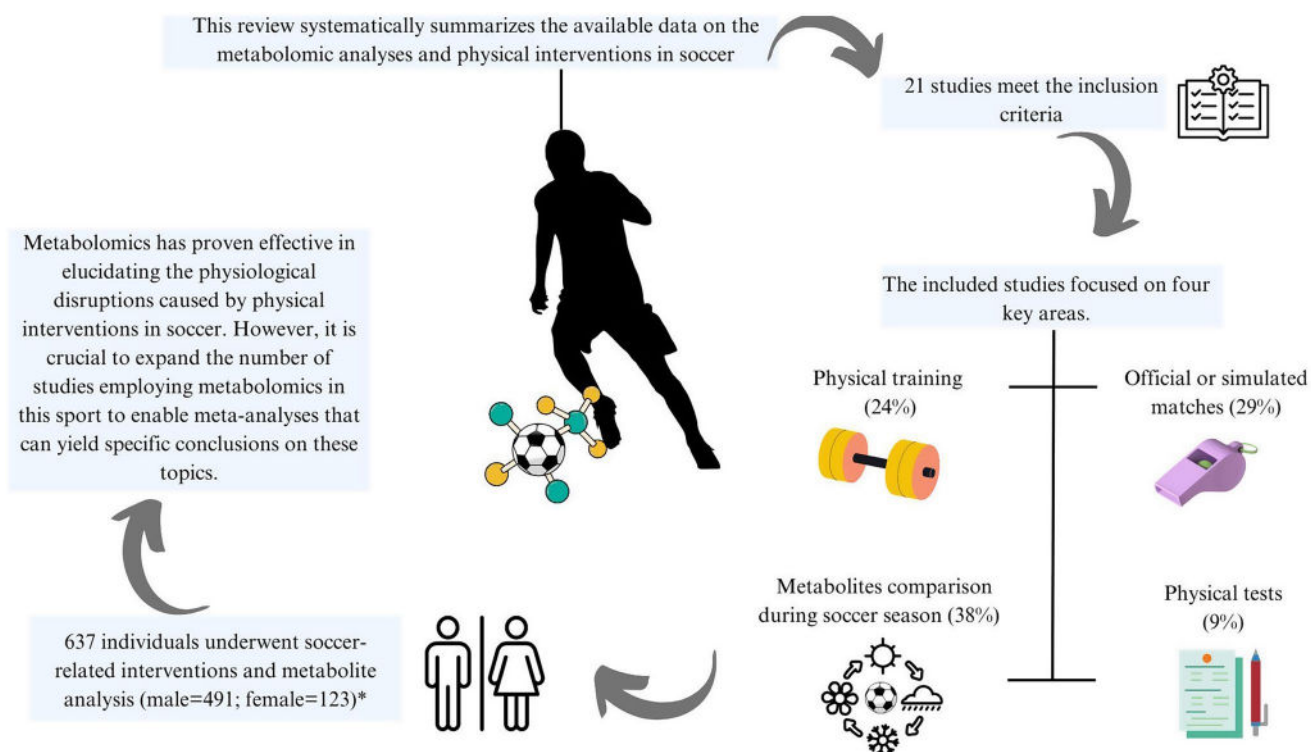
<sup>1</sup>H-NMR - Proton Nuclear Magnetic Resonance; UHPLC-MS - Ultra-High Performance Liquid Chromatography-Mass Spectrometry. ESI - Electrospray Ionization

effectively distinguishing athletes based on their performance in the Yo-Yo test. Further, Cruz et al. (2022) found that serum metabolites classified as Glycerophospholipids, Glycerophosphoglycerols, Phosphatidylethanolamines, Phosphatidylcholines, Cardiolipins, Glycerolipids, Flavonoids, Sterol Lipids, and Fatty Acyls showed high variable importance in projection scores inside the Partial Least Squares Discriminant Analysis model when comparing elite and non-elite athletes. This indicates that these molecules were crucial for distinguishing these groups, even when anthropometric variables and aerobic capacity were similar. Although only two studies were eligible within this realm, it is possible to suggest that the metabolome can differentiate soccer players with varying levels of performance or physical fitness.

The eligible studies that employed metabolomic analyses over the soccer season had different objectives, although most of them used urine as the matrix of choice. Since metabolites identified during pre-season by Pintus et al. (2021) were associated with factors such as diet, training, and microbiota, these authors discuss possibilities such as developing a kit for real-time monitoring of athletes' responses to training and nutrition, with the goal of enhancing performance, managing exercise-induced muscle damage, and tailoring nutritional strategies according to athletes' metabolomic profiles. Studying various points throughout a season, Quintas et al. (2020) observed a significant association between external load and urinary metabolites, with alterations in biochemical pathways linked to long-term training adaptation. The authors suggest that future studies should aim to validate these findings to identify professional soccer players at risk of developing muscle injuries. Although the objective of Rodas et al. (2022) primarily focuses on the effects of training, it is worth noting that urine metabolites were also associated with external load to assess athletes' adaptation to training throughout the season.

Aiming to analyze appropriate recovery times for improving soccer skills, Kim et al. (2022) observed that adenine, 2-hydroxybutyrate, alanine, and lactate increased during the 5 days of recovery following the winter training season. Based on the assumption that these molecules are associated with post-exercise physiological recovery, the authors suggest at least 5 days of recovery time after the training period. Focusing on fluctuations in vitamin D levels and its metabolites over the course of half a season, Ksiazek et al. (2023) found no evidence that free 25-(OH)D measurements are superior to total 25-(OH)D in relation to psychophysical stress markers. Additionally, 25-(OH)DT and 25-(OH)DF did not influence testosterone levels in soccer players across various training periods, besides training loads did not affect resting concentrations of vitamin D metabolites. With a unique perspective among the eligible studies, Peña et al. (2023) monitored the lipid profile of mature erythrocyte membranes in professional female athletes over three seasons. The modulations observed revealed metabolic markers of intense exercise, inflammation, and oxidative stress throughout the season, suggesting the need for personalized nutrition strategies for female soccer players.

The last two studies present distinct objectives; however, like the other studies in this context, they offer practical relevance. Gouveia et al. (2024) observed that across three championship matches, female soccer players showed a significant shift in their pre- and post-game metabolomic profiles. This variation could be influenced by various factors, including the characteristics of the opposing team, the buildup of fatigue throughout the tournament, and the results of each match. Gonzalez et al. (2024) found that beta-alanine was linked to a reduced risk of injury, whereas serotonin and 5-hydroxy-tryptophan were associated with a higher likelihood of injury. All these factors are of interest in the science surrounding soccer (Caruana-Bonnici et al., 2019; Hader et al., 2019; Jaspers et al., 2017; Nedelec et al., 2012, 2013; Petri et al., 2024; Rollo & Williams, 2023;



**Fig. 2** Overview of the systematic review. \*One study did not report the sex of the participants, which had a sample size of 23

Viciani et al., 2022). In this way, the insights provided by the mentioned eligible studies reinforce interests already established by the scientific community regarding soccer, highlighting that metabolomics analyses can be valid for this purpose.

Metabolomic analyses provide a broad-spectrum overview of physiological modulations in soccer athletes. However, their practical application depends on bridging the gap between the highlighted analytical techniques in this review and the day-to-day needs of teams. Unlike established serum markers, such as lactate or glucose, metabolomics face challenges in providing rapid feedback for the team staff. Nonetheless, their practicality may be enhanced through specific biological matrices. This review revealed that urine was the most commonly used physiological matrix, followed by saliva, both facilitating closer field-lab integration due to easier biological material collection when compared to total blood, plasma, or erythrocytes. Determining the most suitable biological matrix for metabolomic analysis in the daily context of soccer remains an open question, heavily dependent on the specific needs and conditions of each team. It is crucial to consider not only the invasiveness of sampling each matrix but also the frequency of sampling and the specific insights that metabolomics can offer to effectively support coaches and sports scientists. Regardless of the biological matrix selected, the data provided by metabolic markers can potentially aid in identifying early signs

of fatigue, overtraining, and nutrient deficiencies, ultimately helping to optimize recovery, refine training strategies, and reduce the risk of injuries in soccer players. This systematic review also underscores that while there is progress to be made in applying metabolomic analyses on the field, prioritizing biologically accessible matrices is a strong starting point.

This systematic review is not free of limitations. The variability in biological matrices, analytical methods, and types of interventions restricts the ability to conduct a meta-analysis. Moreover, the literature produced to date has predominantly focused on male athletes. However, one of the few studies comparing male and female athletes have shown they present different changes in the urinary metabolome associated to exercise external load along a season, mainly linked to the Tryptophan, Cysteine and methionine metabolisms, Purine metabolism, and Arginine and aminoacyl-tRNA. That said, it is unlikely results with male athletes can be directly replicated for females, and future studies should focus on that cohort. Another point worth highlighting is that clear information on the athletes' hydration levels was presented in only one study. Especially in reports using urine as a biological matrix, this factor should be better controlled in future studies. Urine shows substantial fluctuation in concentration and composition within individuals over relatively short periods, underscoring the importance of this consideration (Nam et al., 2020). Regarding the strengths,

all steps were conducted following well-established guidelines in the scientific community, such as PRISMA. The screening process was carried out by three researchers, and the majority of the eligible studies demonstrated excellent methodological quality. It should be emphasized that this is the first systematic review on the subject, with its main contribution being the identification of gaps that persist regarding the application of metabolomics sciences to understand the physiological responses of soccer players subjected to physical interventions, whether through training sessions, physical tests, matches, or even throughout the season. Future studies should consider female athletes, explore the relationship between metabolites and soccer performance more deeply, and examine the effects of different training periodizations on these markers.

## 5 Conclusion

Figure 2 summarizes the main findings of this study. This systematic review reveals that metabolomics research in soccer mainly targets metabolite analysis across competitive seasons, with additional studies investigating profiles during official matches, training sessions, and physical tests. The review provides a comprehensive analysis of the current understanding of metabolomics in this sport, highlighting critical gaps for further exploration. Expanding metabolomics studies with standardized methodologies is essential for building a robust evidence base, facilitating meta-analyses, and advancing knowledge in this metabolomics-soccer realm.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

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