

Use of Complementary Medicine in Competitive Sports: Results of a Cross-Sectional Study

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Keywords

Elite athletes · Complementary medicine · Integrative medicine · Sports medicine

Abstract

Background: Although complementary medicine is frequently used in Germany, there is almost no information about complementary medicine use in competitive sports. The aim was to assess the use of complementary medicine among elite athletes in Germany. **Patients and Methods:** A cross-sectional study among athletes was performed between March 2012 and September 2013. Athletes of both sexes who visited a sports medical outpatient clinic in Munich, Bavaria were included. Data about the use of complementary medicine were collected by means of a standardized measurement instrument, the German version of the international complementary and alternative medicine questionnaire. **Results:** Of the 334 athletes (female 25%, mean age 20.2 ± 6.6 years) who completed all 4 sections of the questionnaire, 69% reported the use of at least one type of complementary medicine within the last 12 months. 505 athletes (female 26%, mean age 20.5 ± 7.0 years) completed at least one section of the questionnaire entirely. Within 12 months, the osteopath (11%), herbal medicine (17%), vita-

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mins/minerals (32%), and relaxation techniques (15%) were the most frequently visited/used in relation to the respective sections of the questionnaire. **Conclusion:** Complementary medicine is frequently used by athletes in Germany. The efficacy, safety, and costs of complementary medicine should be investigated in clinical trials among athletes in the future.

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Die Verwendung von Komplementärmedizin im Leistungssport: Ergebnisse einer Querschnittsstudie

Schlüsselwörter

Leistungssportler · Komplementärmedizin · Integrative Medizin · Sportmedizin

Zusammenfassung

Hintergrund: Obgleich die Komplementärmedizin in Deutschland häufig eingesetzt wird, gibt es fast keine Informationen zum Einsatz im Bereich des Leistungssports. Ziel war es daher, den Einsatz der Komplementärmedizin bei Leistungssportlern in Deutschland zu untersuchen. **Patienten und Methoden:** Eine Querschnittsstudie unter Leistungssportlern wurde zwischen März 2012 und September 2013 durchgeführt. Eingeschlossen wurden Leis-

tungssportler beiderlei Geschlechts, die eine sportmedizinische Ambulanz in München, Bayern besuchten. Angaben zur Nutzung von Komplementärmedizin wurden mit Hilfe eines standardisierten Messinstruments, der deutschen Version des internationalen Fragebogens für Komplementär- und Alternativmedizin, erhoben. **Ergebnisse:** Von den 334 Leistungssportlern (25% weiblich, Durchschnittsalter $20,2 \pm 6,6$ Jahre), welche alle vier Abschnitte des Fragebogens ausgefüllt hatten, gaben 69% an, innerhalb der letzten 12 Monate mindestens eine Art von Komplementärmedizin angewendet zu haben. 505 Leistungssportler (26% weiblich, Durchschnittsalter $20,5 \pm 7,0$ Jahre) füllten mindestens einen Abschnitt des Fragebogens vollständig aus. Innerhalb der letzten 12 Monate wurden, in Bezug auf die jeweiligen Abschnitte des Fragebogens, der Osteopath (11%), die Phytotherapie (17%), Vitamine und Mineralien (32%) und Entspannungstechniken (15%) am häufigsten besucht/verwendet. **Schlussfolgerung:** Komplementärmedizin wird von Leistungssportlern in Deutschland häufig eingesetzt. Die Wirksamkeit, Sicherheit und Kosten der Komplementärmedizin sollten in Zukunft in klinischen Studien bei Sportlern untersucht werden.

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Introduction

Complementary medicine (CM) includes a broad set of health care practices that are not part of conventional medicine and is not fully integrated into the dominant health care system. The terms are used interchangeably with traditional medicine in some countries [1]. CM is experiencing a growing popularity [2], and its utilization in the general population ranges internationally between 5 and 75% [3]. It depends, among other things, on laws and reimbursements in the health care systems [4]. More than 60% of respondents in the general population in Germany use at least one of the CM fields “natural remedies and herbal medicines,” “natural healing methods,” “homeopathic medicine,” “relaxation techniques,” “acupuncture and Chinese Medicine,” and “chiropractic and osteopathy” [2, 5]. In addition, up to 60% of German physicians offer CM or refer to it [6]. Elite athletes (hereafter referred to as athletes) experience high training loads and often use CM for the prevention and treatment of diseases [7]. Fifty-six percent of US college athletes reported the use of CM within the past 12 months [8]. In Germany, a study in 110 athletes (63% male, 37% female; age 24.3 ± 5.0) with high performance levels in Olympic sports found a 97% use of CM and/or physiotherapeutic methods [9]. However, results of the use of CM among athletes in a larger population using a standardized measurement instrument are not published yet to the best of the authors’ knowledge. The aim of the

cross-sectional study was to assess the use of CM and its practical application among athletes in a large athlete population of different professional sports by using a standardized measurement instrument in Germany.

Methods

Study Design

A cross-sectional study on the utilization of CM among athletes was performed between March 2012 and September 2013 by consecutive recruitment.

Inclusion and Exclusion Criteria, Setting

During the period of investigation, all athletes who attended the annual pre-participation screening at the outpatient clinic of the Center for Prevention and Sports Medicine at the Technical University of Munich, Germany were approached. Eligible for inclusion were all athletes of both sexes without age restriction who were members of the national team or, in the case of soccer players, adolescent and adult athletes. Athletes in disabled sports were also included. Specific exclusion criteria did not exist.

Outcome Measurement and Data Collection

Data about the use of CM were collected by the standardized international complementary and alternative medicine questionnaire (I-CAM-Q) [10, 11] in its German version I-CAM-G [12]. The questionnaire was either completed directly on site or taken home to fill out. Some young participants completed the questionnaire in the presence of or with the help of their parents. To obtain results about the use of CM, all eligible athletes were asked to complete the questionnaire even if they had not used any CM. The completed questionnaires were received at the center without checking for uncompleted parts of the questionnaire. The acceptance of unfilled portions led to missings in the data. The I-CAM-G contains 4 sections assessing the prevalence of CM use, the reason for CM use, and how helpful it was [12]. The I-CAM-G section 1, listed below as “CM provider,” elicits information about visiting health care providers, referring to physicians and non-physicians, treating the respondent with CM. The I-CAM-G section 2, “CM treatment,” obtains information about complementary treatments received from physicians. The I-CAM-G section 3, “herbal medicine and dietary supplements,” acquires data on the use of prescribed and self-medicated herbal medicines and dietary supplements in any form. The I-CAM-G section 4 gathers information about “self-help practices.” Only data about CM use and its perceived efficacy within the previous 12 months are reported here, as only these sections were filled out consistently. Data from each of the 4 sections of the I-CAM-G are reported with regard to the number of athletes who answered the respective section. To calculate the “overall CM use” across all respondents, only the participants who filled out all 4 sections regarding CM use within the last 12 months were analyzed. In addition, data about age, sex, and sport-specific information were assessed.

Data Analysis and Statistics

Sample size calculation was not performed. The data input was conducted with the help of an online questionnaire (SoSci Survey) [13]. A descriptive statistical analysis of absolute and relative frequencies of CM use was performed using IBM SPSS for Windows version 24 [14] and SAS for Windows (version 9.4) [15]. Regarding missing data, no imputation was done. Additionally, stratified analyses were performed using the variables sex, age (groups: <18 years, 18 to <25 years, 25 to <35 years, and ≥ 35 years), and sports category (groups: team and individual sports).

Table 1. Characteristics of the study population

	N	N (%) / mean \pm SD
Age	485	20.5 \pm 7.0
Age groups	505	
Under 18		201 (39.8)
18 to 24		178 (35.2)
25 to 34		86 (17.0)
35 and older		20 (4.0)
Unknown		20 (4.0)
Sex	505	
Male		348 (68.9)
Female		130 (25.7)
Unknown		27 (5.3)
Education	505	
Lower secondary school		26 (5.1)
Intermediate school		112 (22.2)
High School		148 (29.3)
Other degree		3 (0.6)
No degree		173 (34.3)
Unknown		43 (8.5)
Most frequent sports disciplines	505	
Soccer		138 (27.3)
Ice hockey		49 (9.7)
Bobsleigh		41 (8.1)
Figure skating		24 (4.8)
Luge		22 (4.4)
Shooting		20 (4.0)
Snowboard		17 (3.4)
Ski freestyle		16 (3.2)
Skicross		16 (3.2)
Athletics		14 (2.8)
Individual versus team sport	505	
Individual sport		220 (43.6)
Team sport		260 (51.5)
Unknown		25 (5.0)
Training frequency, per week	505	
3 times		56 (11.1)
More than 3 times		252 (49.9)
Daily		174 (34.5)
Unknown		23 (4.6)
Training duration, usually per unit	505	
<2 h		196 (38.8)
2–3 h		264 (52.3)
>3 h		19 (3.8)
Unknown		26 (5.1)

SD, standard deviation.

Results

Study Participants

From March 2012 to September 2013, 505 athletes, including 130 (26%) female and 348 (67%) male ($n = 27$, 5% did not specify their sex), completed at least one section of the I-CAM-G regarding CM use within the last 12 months (Table 1; Fig. 1). The participants had a mean age of 20.5 ± 7.0 years (median 18.0 years) and 40% were younger than 18 years old. In contrast, all 4 sections of the I-CAM-G were filled out completely by 334 athletes (fe-

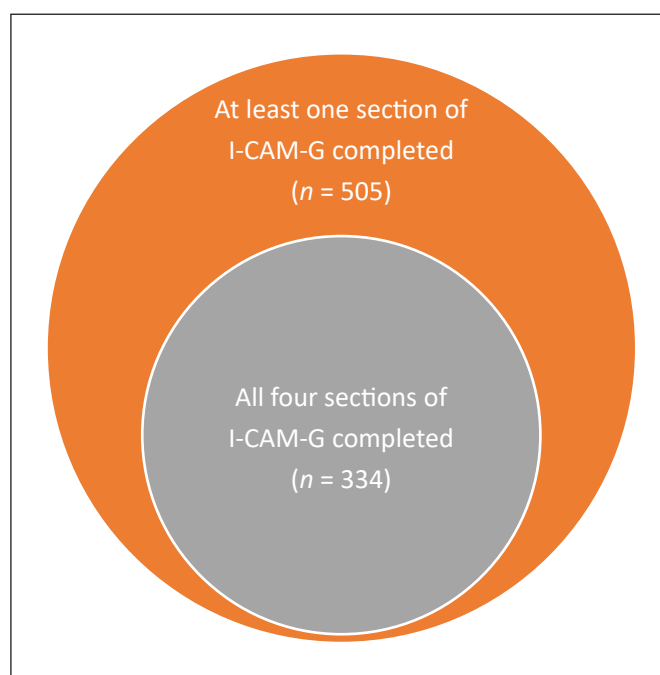


Fig. 1. Number of athletes who completed all 4 sections of the I-CAM-G with regard to athletes who completed at least one section of the I-CAM-G.

male $n = 83$, 25%; male $n = 234$, 70%; not specified $n = 17$, 5%), with a mean age of 20.2 ± 6.6 years (median 18.0 years).

Use of Complementary Medicine

Only a few therapists or therapies were indicated, the most frequent of which are listed below. The most often visited CM provider was an osteopath (11%), and the most often used CM treatment was herbal medicine (17%) followed by manual therapy (16%). Regarding I-CAM-G section 3, vitamins/minerals (32%) were most often used, and the most frequent self-help practices were relaxation techniques (15%; Table 2). Within the I-CAM-G sections, the most rated as “very helpful” by the respective users were the osteopath and the chirotherapist (each 75%), Traditional Chinese Medicine (TCM, 100%), herbal medicine (64%), and visualization (65%). However, in some categories, only a few respondents used the respective methods and rated their helpfulness; for example, TCM was rated 100% helpful by only 7 users. Most athletes rated CM as “helpful” in all 4 sections.

Concerning the overall CM use within the last 12 months, 69% of the 334 athletes who filled out all 4 sections of the questionnaire reported the use of CM. Specifically, 29% of these athletes visited a CM provider, 36% used CM treatments, 49% used herbal medicine and dietary supplements, and 32% applied self-help practices. The overall CM use according to sex, age, and individual

Table 2. I-CAM-G results of all responding participants

	Visits/treatments		Evaluation			
	last 12 months, <i>n</i> (%)	<i>n</i>	very helpful, <i>n</i> (%)	somewhat helpful, <i>n</i> (%)	not helpful, <i>n</i> (%)	don't know, <i>n</i> (%)
Section 1: CM provider (<i>n</i> = 503)						
Homeopath (physician)	39 (7.8)	39	19 (48.7)	16 (41.0)	2 (5.1)	2 (5.1)
Acupuncturist (physician)	20 (4.0)	19	12 (63.2)	3 (15.8)	1 (5.3)	3 (15.8)
Physician CM	24 (4.8)	23	9 (39.1)	9 (39.1)	2 (8.7)	3 (13.0)
Non-medical health provider (“Heilpraktiker”)	45 (8.9)	40	27 (67.5)	10 (25.0)	2 (5.0)	1 (2.5)
Osteopath (physician or non-physician)	55 (10.9)	52	39 (75.0)	11 (21.2)	1 (1.9)	1 (1.9)
Chirotherapist (physician or non-physician)	17 (3.4)	16	12 (75.0)	4 (25.0)	0	0
Other (physician or non-physician)	16 (3.2)	15	11 (73.3)	4 (26.7)	0	0
Section 2: CM treatment (<i>n</i> = 398)						
Homeopathy	44 (11.1)	37	16 (43.2)	18 (48.7)	2 (5.4)	1 (2.7)
Acupuncture	14 (3.5)	12	9 (75.0)	3 (25.0)	0	0
Herbal medicine	67 (16.8)	59	31 (52.5)	26 (44.1)	0	2 (3.4)
Manual therapy	64 (16.1)	58	44 (75.9)	12 (20.7)	1 (1.7)	1 (1.7)
Traditional Chinese Medicine	7 (1.8)	7	7 (100)	0	0	0
Other	6 (1.5)	5	4 (80.0)	0	1 (20.0)	0
Section 3: herbal medicine and dietary supplements (<i>n</i> = 427)						
Homeopathic remedies	76 (17.8)	76	44 (57.9)	38 (50.0)	2 (2.6)	10 (13.2)
Herbs/herbal medicine	70 (16.4)	70	45 (64.3)	34 (48.6)	0	8 (11.4)
Vitamins/minerals	136 (31.9)	136	71 (52.2)	59 (43.4)	1 (0.7)	18 (13.2)
Other	25 (5.9)	25	13 (52.0)	10 (40.0)	1 (4.0)	2 (8.0)
Section 4: self-help practices (<i>n</i> = 475)						
Meditation	25 (5.3)	21	13 (61.9)	7 (33.3)	1 (4.8)	0
Yoga	34 (7.2)	26	13 (50.0)	10 (38.5)	3 (11.5)	0
Qigong	9 (1.9)	7	1 (14.3)	4 (57.1)	1 (14.3)	1 (14.3)
Tai Chi	1 (0.2)	1	0	1 (100)	0	0
Relaxation techniques	71 (14.9)	57	30 (52.6)	25 (43.9)	2 (3.5)	0
Visualization	40 (8.4)	35	23 (65.7)	12 (34.3)	0	0
Praying for own health	45 (9.5)	36	17 (47.2)	11 (30.6)	0	8 (22.2)
Paint/make music for own health	19 (4.0)	17	8 (47.1)	7 (41.2)	0	2 (11.8)
Other	17 (3.6)	17	12 (70.6)	4 (23.5)	1 (5.9)	0

CM, complementary medicine; *n*, number of respondents.

Table 3. CM overall use results of respondents who filled out all 4 sections of the I-CAM-G

	<i>N</i>	CM overall use, <i>n</i> (%)
Age groups (<i>n</i> = 320)		
Under 18	134	83 (61.9)
18 to 24	120	84 (70.0)
25 to 34	55	50 (90.9)
35 and older	11	7 (63.6)
Sex (<i>n</i> = 317)		
Male	234	154 (65.8)
Female	83	69 (83.1)
Team vs. individual sport (<i>n</i> = 315)		
Team sport	185	115 (62.2)
Individual sport	130	106 (81.5)

CM, complementary medicine.

versus team sports is provided in Table 3. Of the respondents, patients with the following characteristics used CM most frequently: 25–34 years old (90.9%), women (83.1%), and individual athletes (81.5%).

Stratified Analysis

Based on the completed data, the CM usage by various groups is briefly reported below.

Sex

Females most often visited an osteopath (16%), while males most often visited a non-medical health provider (“Heilpraktiker”) (10%). Females preferred herbal medicine (25%) in contrast to manual therapy for males (16%). Both females (40%) and males (29%) favored vitamins/minerals and relaxation techniques.

Age

Athletes younger than 25 years most often visited a non-medical health provider (<18 years 8%; 18 to <25 years 9%), and all other athletes visited most often the osteopath (25 to <35 years 24%; ≥35 years 20%). Younger athletes most frequently applied herbal medicine (<18 years 15%; 18 to <25 years 21%), while older athletes most commonly used manual therapy (25 to <35 years 30%) or manual therapy and acupuncture (≥35 years of age 20%). Among all age groups, vitamins/minerals were used the most, increas-

ing according to the age groups (28–53%). Athletes <18 years most frequently used praying for their own health (11%), and adult athletes used relaxation techniques, increasing with the respective age groups (20–28%).

Individual Sports and Team Sports

A total of 480 athletes reported competing in their sport in 38 disciplines. 220 athletes ($n = 135$ male, $n = 85$ female; mean age 21.9 ± 7.9 years, median age 19.5 years) performed an individual sports discipline, while 260 athletes ($n = 211$ male, $n = 42$ female, $n = 7$ did not specify their sex; mean age 19.3 ± 6.0 years, median age 18.0 years) performed a team sports discipline.

Athletes in individual sports most likely visited an osteopath (15%) but also frequently a homeopath (14%) and a non-medical health provider (13%). However, athletes in team sports most frequently visited an osteopath (7%), a non-medical health provider (6%), and an acupuncturist (4%). Athletes in individual sports used mostly herbal medicine (26%) and manual therapy (21%), while athletes in team sports similarly often used manual therapy (13%) and herbal medicine (11%). Vitamins/minerals were used the most by athletes in individual (35%) and team sports (30%). Athletes in individual sports applied relaxation techniques most often (24%), while athletes in team sports used “praying for their own health” (10%).

Discussion

The present cross-sectional study provides an overview of the CM usage behavior within 12 months of more than 500 athletes in Germany. Osteopaths were visited most often, and herbal medicine, vitamins/minerals, and relaxation techniques were used most frequently. Among the athletes who completed all 4 sections of the questionnaire, 69% reported the use of at least one type of CM.

The present study is, to our knowledge, the first comprehensive overview of CM utilization using a standardized questionnaire in more than 500 athletes in Germany. Further, the inclusion criteria were very broad and pragmatic, and therefore, athletes from a wide spectrum of sports disciplines were included. The main limitation, caused by the pragmatic distribution strategy, was that we were not able to calculate the response rate and that we could only use an expedient method. This bias could lead to an overestimation of CM use because it might be that we obtained more responses from users than non-users of CM. A further limitation of our pragmatic study was that the questionnaires were often not filled out completely, which could be due to lack of time or lack of interest on the part of the athletes. This could lead to an underestimation of CM use. Therefore, we could only obtain

reliable data for at least one section of the I-CAM-G within the last 12 months for 505 athletes. Although the study was monocentric with the recruitment occurring in Bavaria, Germany, German top athletes from mostly southern Germany were included, but no general conclusions for Germany are possible.

According to the present study, the overall CM use among professional athletes within the last 12 months is 69%, which mirrors the CM use among the general population in Germany (up to 63%) [2, 5]. In the analysis of the 2012 National Health Interview Survey (NHIS) in the US, of 34,518 general population participants, 10,158 (median age 46.5 years) responded to the questions on the use of CM [16]. In contrast to our results, of these, only 21% reported CM use for improvement in athletic performance [16].

In competitive sports, a former, small cross-sectional study in Germany found that 97% of athletes in Olympic sports with high performance levels use CM ($n = 110$, 63% male, 37% female; age 24.3 ± 5.0 years) [9]. However, in contrast to the study presented here, the authors of this smaller trial included the use of sports nutrition (60% use), sports drinks (59% use), and sports functional clothing (34% use) as well as the use of energy bracelets (24%), physiotherapy (92% use), and physiotherapeutic procedures such as electrotherapy and thermotherapy [9]. In contrast, the present study used the I-CAM-G. The fact that the above-mentioned methods are not included in the I-CAM-G and that the free text option was often not used could be considered the main reason for the different results in overall CM use between the former trial [9] and the present study.

The results of this study concerning the visited CM providers differ from available data in the general population in Germany, in which a physician with qualifications in naturopathy (11%), followed by a non-medical health provider (6%) and a physician with qualifications in homeopathy (6%) were the most visited CM providers within the last 12 months. Visiting an osteopath was not assessed by Härtel and Volger [2], while in the present study, the osteopath was the most visited CM provider. The Forsa survey about the use of osteopathy in Germany in 2018 reported that 21% of 2,218 participants in the general population were treated by an osteopath during their lifetime [17]. In Germany, osteopaths are often physiotherapists, non-medical health providers (“Heilpraktiker”), or physicians. The I-CAM-G includes here physicians and non-physicians and does not differentiate which accredited primary medical profession an osteopath holds.

Gerbing et al. [9] assessed the use of manipulative and body-based therapies in athletes and reported that athletes use kinesiotaping (61%) and special functional clothing (34%) more often than chiropractic (22%) and osteopathic (20%) providers. On the other hand, although the most visited CM provider in the present study among

all participants ($n = 505$) was the osteopath (11%), and manual therapy (16%) was the second most frequently used CM treatment, both were less visited/used than the CM providers reported by Gerbing et al. [9]. Manual-based therapies are used and accepted in competitive sports for the prevention and treatment of muscle injuries [18]. A retrospective analysis of treatment charts of athletes seeking chiropractic treatment at the world games in 2013 reported that out of 2,964 accredited athletes, 18% used chiropractic care, and 85% reported immediate pain reduction [19]. The use of manual therapy (16%) by athletes in our study corresponds approximately to the usage behavior of the general population in Germany (14%) [2], which rates manual therapy and osteopathy as particularly effective compared to other CM procedures [5]. German general practitioners also rate manual therapy as particularly effective [20]. Club or team physiotherapists are often available in competitive sports, and classical physiotherapy (92%) and sports physiotherapy (73%) [9] are frequently used. However, in the present study, the physiotherapist is not part of the preformulated core list according to the I-CAM-G and has been reported in free text only by some participants. Perhaps this information would have been given more frequently if the answer had been preformulated. On the other hand, physiotherapy in Germany is not a CM procedure [21]. Likewise, kinesiotaping, kinesiology, and functional clothing are not preformulated in the I-CAM-G, and the opportunity to report these in free text was rarely used. Eight percent of athletes taking part in the present study reported visiting a homeopath, while 11% used homeopathy within the last 12 months. In Germany, even physicians without special training prescribe homeopathic remedies [5]. In addition, it can be assumed that homeopathic remedies could be used by the athletes as self-therapy, although the I-CAM-G inquires about therapies provided by physicians. Gerbing et al. [9] found a more common use of homeopathy (44%). We found a frequent use of herbal medicine by athletes (17%), and in the general population in Germany, treatments with herbal medicine (28%) are used more often [2].

The athletes reported a relatively small use of vitamins/minerals (32%) in contrast to our expectations and in comparison with Gerbing et al. [9], who found 88% use of food supplements in competitive athletes. A total of 60% of professional athletes individually decide on their use of vitamins/minerals, sports nutrition, and sports drinks [9]. A study published in 2004 by Geyer et al. [22] found that in 15% of 634 investigated food supplements purchased in various countries, anabolic androgenic steroids were not declared on the label (“positive supplements”). As this may result in unintentional positive doping test results, it can only be assumed that the athletes in the present study tried to avoid (or avoid reporting) those

types of food supplements. However, only a few food supplements were found to have strong evidence to support efficacy and safety in muscle building and performance enhancement [23]. We found a frequent use of relaxation techniques by 15% of athletes, while approximately 8–9% of the general population in Germany uses relaxation techniques [2, 5]. Visualization was the second most frequent self-help practice (8%) within the presented population. It can be used to improve health and well-being and is predefined in the I-CAM-G for the general population. Modern competitive sports use visualization techniques to optimize concentration and focus in children, adolescents, and adults [24–26].

Our study results indicated that the majority of athletes used CM in Germany but with unclear effects. Further cross-sectional studies about CM use should focus on minimizing missing data, for example, by reviewing the returned questionnaires immediately or contacting respondents to ask about missing items. Electronic questionnaires could be programmed to only proceed after complete answers. Further studies should not only focus on the correlation between the type of sport practiced and the complementary therapy used, but also on the clinical problem for which the therapy is preferred; it could be an important indication for the whole sporting world and also indirectly of its therapeutic efficacy. Further studies about CM use in athletes should focus on CM use in specific sports disciplines and investigate the treatment effects, safety, and costs of CM in athletes. This could be realized as a first step by high-quality multicenter cohort studies with a sample size calculation based on prior results measuring participant-reported outcomes and “objective” medical data. In a second step, prospective intervention studies should verify the results of the cohort studies. However, the most important outcome in competitive sports is good athletic performance; this outcome seems to be difficult to measure in relation to CM.

Conclusion

CM is frequently used by German athletes and rated as helpful. The most often visited or used types of CM were osteopaths, herbal medicine, vitamins/minerals, and relaxation techniques. As the effects of CM in athletes remain controversial, further research should focus on CM use in specific sports disciplines and should investigate treatment effects, safety, and costs with clinical studies.

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Statement of Ethics

As there was no risk to study participants and it was not required for this study type, no ethics vote was obtained. The questionnaires were pseudonymized, processed in accordance with the ethics guidelines, and are published anonymously. The participants have agreed to the survey within the scope of their patient consent.

Conflict of Interest Statement

No competing financial interests exist.

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G.R. interpreted the data and drafted the manuscript. L.S. collected data and partly carried out the study. S.B. performed data management, contributed to the interpretation of the data, and revised the manuscript. C.D. carried out the statistical analyses, interpreted the data, and revised the manuscript. J.S. contributed to the interpretation of the data and revised the manuscript critically. F.P. conceived and coordinated the study, contributed to the interpretation of the data, and revised the manuscript. B.B. contributed to the interpretation of the data and revised the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.