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Menstrual Dysfunction as the Leading Clinical Marker for the Future Development of the Female Athlete Triad: a Meta-Analysis

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MENSTRUAL DYSFUNCTION AS THE LEADING CLINICAL MARKER FOR THE FUTURE DEVELOPMENT OF THE FEMALE ATHLETE TRIAD: A META-ANALYSIS

by

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MENSTRUAL DYSFUNCTION AS THE LEADING CLINICAL MARKER FOR FUTURE DEVELOPMENT OF THE FEMALE ATHLETE TRIAD: A META-ANALYSIS

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The Female Athlete Triad is a diagnosable medical condition that is under researched and very prevalent in female sports today. The development of the Female Athlete Triad, or any of its components, can negatively impact many aspects of a female athlete's life. If clinical markers could be identified that indicate future development of the Triad, it could potentially help prevent occurrence of the condition and greatly reduce the number of female's that have to suffer from it. Menstrual dysfunction could be the leading clinical marker for the future development of the Triad. This meta-analysis seeks to explore the possible association of menstrual dysfunction and the development of the Female Athlete Triad

Chapter 1. Introduction

1.1 The Female Athlete Triad

In our modern world, the prevalence of female athletes is rapidly growing and has been for many years. With Title IX and the inclusion of female sports in many school programs, female athletics are at an all-time high. This is something to be celebrated, but does come with certain medical conditions that are not seen in male counterpart sports. At this point, there is still limited research on many conditions specific to female athletes. One such condition is The Female Athlete Triad. The Female Athlete Triad (the Triad) is a condition that is perpetuated by multiple risk factors, with one of the most common ones potentially being a history of menstrual dysfunction. The Triad became a diagnosable condition in 1992 when it was defined by the American College of Sports Medicine as amenorrhea, osteoporosis and disordered eating.[1] The Triad has recently changed how it defines the three clinical components that make it up, from amenorrhea to menstrual dysfunction, from osteoporosis to decreased bone mineral density, and from disordered eating to low energy availability (with or without an eating disorder). There are many risk factors that can perpetuate the development of the Triad, and this meta-analysis seeks to demonstrate that menstrual dysfunction is the leading clinical marker for future development of the Triad.

1.2 Literature Review

1.2.1 Overview of the Female Athlete Triad

The Female Athlete Triad has the potential to effect an incredibly large population. Each component of the Triad has been found to have a significantly higher rate of development in athletes than it does in the general female population. Female athletes have a prevalence of amenorrhea at rates as high as 69%, compared to 5% in the general female population.[1] They can also have a prevalence of up to 47% for disordered eating, as compared to the general female population rate of up to 10%.[1] The prevalence of low bone mineral density in female athletes has been found to be up to 50%, which in the general female population only reaches up to 12%.[1] Many of the symptoms of and ultimate diagnosis of the Triad occurs in female athletes who are involved in sports that are focused on appearance, but are not limited to this population. It can be difficult to see the effects of the disorder immediately as well, as the components fluctuate and move along a spectrum according to energy availability, menstruation, and exercise.[2] Menstrual status may not be evident until up to a month after the development of the disorder, and the effects on bone mineral density may not be evident up to a year.[2]

1.2.2 Components of the Female Athlete Triad

All of the Triad components are inter-related and have the possibility of effecting/causing the others to occur. Menstrual dysfunction in the Female Athlete Triad can be seen in many different disorders. The most common being amenorrhea, in-ovolution and oligomenorrhea.[1] Amenorrhea is the absence of menses for three months or more, and can have two phases. Primary amenorrhea is a delay in menarche, with no menses by age 15 with normal secondary development, and secondary amenorrhea is a loss of menses after menarche has already begun.[1]The causes of menstrual dysfunction are varied. In the general population, the cause is usually due to genetic abnormalities. In athletes, the cause can usually be attributed to energy deficiency and/or stress.[1] There is a specific type of amenorrhea that results from energy deficiency called functional hypothalamic amenorrhea (FHA). This is characterized by amenorrhea due to suppression of the hypothalamic-pituitary-ovarian axis without an organic cause.[1] This type of amenorrhea reflects a bodily state of estrogen deficiency, which, as we will discuss later, can lead to decreased bone mineral density. Menarche also signals normal bone mass growth in adolescents, which, if disrupted in any way, will effect their overall bone mineral density. Menstrual dysfunction has impact on both other components of the Triad in a very large way.

Low energy availability adversely effects the general population, but especially athletes. Energy availability is defined as the amount of energy for all physiological functions after accounting for energy expenditure from exercise. In normal athletes, energy balance should hover around 45 kcal per kg of free fatty mass per day; when these values fall below 30 kcal per day, reproductive and bone function are reduced to restore energy balance.[3] The category for that component of the Triad changed from disordered eating to low energy availability with or without an eating disorder to cover a wider variety of eating issues. Researchers have found that many athletes will have low energy availability without being diagnosed with the psychiatric diagnosis of an eating disorder.[1] Those disorders without psychiatric diagnosis are often referred to as eating disorders not otherwise specified, or EDNOS. Low energy availability in athletes can have different causes, such as not attaining their energy requirements, not having the necessary nutritional knowledge, or actively avoiding foods in order to lose or not gain weight. There is a specific type of eating disorder used by some researchers called anorexia athletica, used to describe disordered eating patterns found in female athletes.[1]

Bone mineral density in the female athlete is a major concern. We know that the greatest accumulation of bone mass occurs during puberty, at which time many female athletes are deep in their sport. If an athlete has a delay of menarche as discussed above, it could delay their bone mass growth during puberty. Many researchers have shown that adult bone structure is determined during puberty, and what happens to bone during this time will largely affect the possible prevention of osteoporosis.[4] Bone loss and delay usually does not occur until much later in life, but we have seen in female athletes that this may occur at much younger ages.[1] Bone strength is due to a combination of many different things, including bone mineral density, bone microarchitecture, and bone remodeling. Osteoblasts build bone during bone remodeling, while osteoclasts breakdown bone. If this process is altered in any way, bone mineral density decreases and bone is weakened. Interestingly, in most healthy athletes, bone mineral density is higher than the general population. Specifically, weight bearing activities are beneficial to females to achieve optimal bone health, due to the positive osteogenic response.[4] This is cited as one of the many benefits of athletics, specifically for females. However, in combination with menstrual dysfunction, female athletes have even lower bone mineral density (BMD) than the general population.[1] It is also well researched that sex differences in bone qualities in males and females is kinder to males. By puberty, males will have more bone strength then females, and will be less likely to lose it with old age.[4] Also, the most common site for stress fractures in females is the tibia, or the lower leg. As briefly discussed earlier, amenorrhea and menstrual dysfunction can cause estrogen deficiency, putting the athlete in a hypo-estrogenic state. This is detrimental because estrogen is an osteoclast inhibitor, and a lack of estrogen can disrupt bone remodeling.[1] Estrogen has many other functions related to bone mineral density, including an influence on calcium absorption. Researchers have found that amenorrheic athletes can have 2 to 4 times greater risk of stress fracture then those athletes without menstrual dysfunction.[1] Disordered eating also plays a large part in bone strength and health, as low energy intake usually means that there is also a lack of essential macronutrients and vitamins and minerals.

1.2.3 Prevalence

It is difficult for researchers to identify accurately the prevalence of the Triad. Because the Triad clinically presents as a continuum, the actual Triad is significantly under-diagnosed. However, most researchers suggest 1 to 3% of female athletes have been diagnosed with the Triad.[6] As stated earlier, since the introduction and passage of Title IX, there has been a large increase in female sports—namely, a one thousand percent increase in the number of female athletes.[5] Females also have unique challenges that come from their sports, and are often over looked. Especially with the standards of Western society, thinness is considered ideal in women's sports and there is a lot of psychological pressure to perform to show that females can compete as well as men.[5] There are some sports that have a higher prevalence and likelihood of developing the disease. Sports where body image and leanness are considered ideal are the main ones, such as gymnastics, skating, cross country, cheerleading and swimming/diving. There is, however, a significantly higher prevalence of each component of the triad in female athletes as there is in the general population. The American College of Sports Medicine states that "the prevalence of stress fractures in athletes diagnosed with low BMD and menstrual dysfunction may approach a rate of 17%."[6]

1.2.4 Long Term Complications and Clinical Significance

The potential long-term complications of the Triad and its' components are significant. Menstrual dysfunction can have the long-term effect of infertility or, oppositely, premature ovulation causing unplanned pregnancy.[1] Hypo-estrogenic states may cause endothelial dysfunction leading to cardiac disease, as well as elevated low-density lipoprotein.[1] Low bone mineral density and menstrual dysfunction increase the likelihood of suffering a stress fracture, which could lead to osteoporosis and arthritis later in life. The most common site of stress fractures in women is the tibia (lower leg), which accounts for 25% to 63% of all cases.[6] Lowered energy availability can cause nutritional deficits, leading to longer recovery time and inability to maintain muscle mass. Developing the Triad or any of its components can have major psychological impacts, with poor body image, depression and worsened eating disorders stemming from it.[1]

1.2.5 Screening and Diagnosis

Developing one component of the disorder does not necessarily mean that the female athlete will develop all of the components, but if awareness can be brought to the clinical markers of the disorder, clinicians could potentially limit the effects of the disorder to only one component of it. Usually, an athlete will develop one of the components of the Triad, and clinicians will overlook and/or miss completely the fact that the development of one component could lead to develop of the condition as a whole. They will treat the individual component while overlooking the possibility of future development of the Triad as a whole. If the main clinical marker of the Triad could be outlined in the female athlete population, awareness, screening and diagnosis could be improved. Early screening and diagnosis could improve health outcomes later in life, as a suffering from the Triad has or can have lasting consequences on the female athlete. Sports Health, a medical journal on sports medicine, stated that "it is universally accepted that triad prevention, early recognition, and a multidisciplinary treatment plan with a focus on proper nutrition and resumption of menses are extremely important and should be priorities among health care professionals, coaches, and other adults involved in the lives of female athletes."[1] Therefore, if development of the Triad is found to be highly, positively associated with menstrual dysfunction, screening and diagnosis of the Triad could be significantly improved.

1.2.6 Treatment and Prevention of the Female Athlete Triad

Treatment of the Triad can be difficult to manage. If the Triad is caught early enough, there is the chance that some of the effects can be reversed. However, as stated earlier, it is often missed and the female athlete is left dealing with the repercussions of it in their later life. For treatment of the Triad, the healthcare provider will conduct tests to determine the extent of the effect on the individual. Most treatment routes will include nutritional counseling, managing menstrual dysfunction and resumption of menses, and restoring bone mineral health through supplements and rest.[7]

Low energy availability will be treated individually based on the individuals' needs and their body mass index. Signs of low energy availability that may be seen and subsequently treated are bradycardia, lanugo and dehydration.[8] The healthcare provider may also test for kidney, liver and renal function. The goal of treatment for low energy availability is to restore a positive energy balance.[8] This will be done through education, psychological care to restore normal eating behaviors, and healthy weight gain. Usually, the individual with low energy availability will be given an eating plan and training program.

Menstrual dysfunction testing will be performed to determine the hormones that are lowered or missing. A healthcare provider will determine if the cause of dysfunction is due to genetic reasons or due to the Triad. It will then be treated ideally without pharmacologic intervention.[8] The greatest predictor of resumption of normal menses was shown to be weight gain.[8] If the individual has symptoms of estrogen deficiency, it will then be treated pharmacologically if other methods have not worked. Contraceptives are not indicated usually. It is imperative menstrual dysfunction is treated. "If amenorrhea goes untreated, females will continue to lose bone mass at a rate of 2-3% per year."[8]

Low bone mineral density will be tested usually through DXA scans, which use X-ray like technology to show bone mineral density. The goal is to prevent further bone loss and to potentially recover the loss bone mineral density.[8] As stated throughout this paper, all 3 of the Triad components are related, and can be seen in the treatment of low bone mineral density. Studies have shown that weight gain, energy balance, and resumption of menses are key to preventing further bone loss.[8] Another treatment of low BMD is weight bearing exercise and resistance training in combination. Estrogen contraceptives have been shown to not be effective to increase BMD.[8] Vitamin D and calcium supplementation may also be pursued to increase BMD.

1.3 Objectives and Hypothesis

1.3.1 Objectives

This meta-analysis study seeks to highlight one potential leading clinical marker of the Triad, menstrual dysfunction. The overall objective of this meta-analysis is to determine the association between menstrual dysfunction as a clinical marker of future development of the Triad through previous studies. The long-term goal is to enable medical professionals to see a history of or current issue of menstrual dysfunction as a clinical marker of the possibility of developing the Triad, and persuade them to enact preventative measures to prevent the development of it. The central hypothesis is that menstrual dysfunction in female athletes has a negative effect on the female athlete body, and can perpetuate and trigger the development of the Triad. The rationale for the proposed research is the clinical effects that menstrual dysfunction has on the anatomy, physiology and mental health of the young female athlete, and the correlation between these and the development of the Triad. The approach of the present research is to review past studies of the Female Athlete Triad and the predisposing factors of those who developed it, to identify if the leading positive correlation exists between menstrual dysfunction and development of the condition. Throughout all the literature research, the greatest risk factor for all three components of the Triad appeared to be menstrual dysfunction.

1.3.2 Hypothesis

The central hypothesis of this study is that menstrual dysfunction in the female athlete can be the leading cause of and can perpetuate or trigger the development of the Triad as a whole. We plan to objectively test the central hypothesis and accomplish our overall objective for this project by pursuing the following two specific aims

1. Investigate the effects that menstrual dysfunction has on bone mineral density and energy availability; and

2. Determine if these effects of menstrual dysfunction perpetuate or trigger the development of the Triad in female athletes.

The working hypothesis of this meta-analysis is that menstrual dysfunction can negatively effect bone health and energy availability of the female athlete, and can be a major cause of triggering the metabolic effects that are risk factors of developing the Triad. The proposal of this meta-analysis is that the effects of the other Triad components on menstrual dysfunction will have less of an impact than the effects of menstrual dysfunction on the other two components.

Chapter 2: Design and Methods

2.1 Subjects

Subjects for this meta-analysis were based on the predisposing characteristics of being current or former female athletes, who were either diagnosed with the Female Athlete Triad, or were treated for one or more of the components of it. There was no age limit for the subjects, as in many cases female athletes did not realize until they were much older and experiencing the consequences of it that they should have been diagnosed with the Triad when they were younger.

2.2 Selection of Studies

Studies that highlighted predisposing factors to developing the Female Athlete Triad as well as studies that looked at post-diagnosis signs and symptoms of the Triad and complications of menstrual dysfunction were identified through a computerized search of the following electronic databases: AgeLine, CINAHL, MedLine, PsycINFO, PubMed, SPORTDiscus, and Web of Science. Articles published from January 1st 2000 to August 1st 2020 were included in this study. Relevant keywords relating to the Female Athlete Triad (‘female,’ ‘athlete,’ ’menstrual dysfunction,’ ‘bone mineral density,’ bone health,’ ‘disordered eating,’ and ‘energy availability’) as well as menstrual dysfunction were used in combination with words related to risk factors and clinical markers.

Two investigators (SH and YW) assessed all potentially relevant articles for eligibility. The decision to include or exclude was made based on the following information: (1) the study title; (2) the study abstract; and (3) the complete study manuscript.

Eligible studies were included if they met all of the following criteria for inclusion: (1) the study had original data; (2) the study showed a correlation between predisposing factors and development of one or more components of the Female Athlete Triad; (3) the research subjects were female athletes; (4) reported all data required for meta-analysis, for interventional studies with experiment and control groups, required data included sample size of experiment group and control group, mean score and standard deviation of pre-test of experiment group and control group; for cross-sectional studies, required data included sample size of both experiment and control groups, mean score and standard deviation of tests of experiment and control groups; (5) article was written in English or translated into English. Studies were not included if they met the following criteria for exclusion: (1) the study did not have original data; (2) the study was just a literature review on the Female Athlete Triad; (3) the research subjects were not female; (4) did not report all the required data for meta-analysis.

2.3 Data Extraction

All data was reviewed and separately extracted by SH and YW using a standardized form that YW previously created in Excel[9]. The following study characteristics were recorded if they were available: author, year of publication, type of study, and place of publication.

2.4 Data Analysis

For each study, an effect size was calculated by a self-developed program in Excel for reported outcome measures of interest.[9] For two-group interventional studies, it expresses the difference of change between pre and posttest between experimental group and control group. For cross sectional studies, effect size is the difference of test scores between two cohorts. A positive value for effect size indicates more favorable outcome scores for the group of interest, and a negative effect size indicates more favorable outcomes for the control group. Usually, researchers define ES as small ($0.2 \leq ES \leq 0.4$), medium or moderate ($0.4 \leq ES \leq 0.6$) and large ($ES > 0.6$) with $p < 0.05$.[10] The analyses of overall ES were implemented using a random effects model.[11]

Chapter 3. Results

3.1 Searching Result

The searches in the electronic databases were performed over a number of days throughout the fall of 2020. We began with a large number of studies, around 50, and through excluding studies with incomplete data and excluding duplication and evaluating titles, abstracts, and text of the articles, eighteen studies were included in this meta-analysis. Among these studies, three were cross-sectional studies ([12-14]), and fifteen were interventional studies ([15-28]).

3.2 Sample Characteristics

3.2.1 Samples

Eighteen studies involving 3,152 participants were finally selected for this meta-analysis; ranging in ages from 13-62, all female, and who played a variety of sports. Participants were involved in basketball, handball, swimming, gymnastics, wrestling, tennis, volleyball, taekwondo, dance, endurance running, cross country, trampolining, aerobics, and cheer. Participants were also involved in secondary school athletics, national team at junior and senior levels, and elite athletics.

Table 3.1 Summary of Eighteen Studies

Study	Type of Study	Mean, SD, Sample size, P value	Sports/Type	Control	Outcome Measure	Tests
Vardar et al. (2005)	Interven-tional	E: n=43, mean=19.6 SD=1.9 C: n=181, mean=20.3 SD=2.1 P=0.01	ALL	without menstrual ir-regularity	low energy availability with men-strual dys-function	BMI
Vardar et al. (2005)	Interven-tional	E: n=43, mean=6.7, SD=6.4 C: n=181, mean=6.5, SD=4.9 P=0.746	ALL	without menstrual ir-regularity	low energy availability with men-strual dys-function	BMI
Valence-Dos-Santos et al. (2018)	Cross Sec-tional	E1: n=20, mean=1.24 SD=0.12 E2: n=26, mean=1.16 SD=0.10 P=0.05	Swimming, Volleyball	low impact sports	low bone mineral density with high impact sports	DXA
Tortstveit et al. (2008)	Interven-tional	E: n=90, mean=20.7 SD=2.10 C: n=96, mean=22.7 SD=2.20 P=0.746	Junior and Senior Na-tional Teams	non-lean sports	low energy availability with lean sports	DXA

Study	**Type of Study**	**Mean, SD, Sample size, P value**	**Sports/Type**	**Control**	**Outcome Measure**	**Tests**
Torstveit et al. (2005)	Interven-tional	E: n=90, mean=20.7 SD=2.10 C: n=96, mean=22.7 SD=2.2 P=0.01	Junior and Senior National Teams	non-lean sports	low energy availability with lean sports	BMI
Tenforde et al. (2018)	Interven-tional	E: n=16, mean=1.96 SD=1.13 C: n=21, mean=0.34 SD=0.92 P=0.746	Collegiate Gymnastics and Swimming	swimming	low bone mineral density with lean sport participation	DXA
Singhal et al. (2019)	Interven-tional	E: n=27, mean=0.94 SD=0.02 C: n=29, mean=0.91 SD=0.02 P=0.02	Weight bearing athletes	eumenorrheic	low bone mineral density with menstrual dysfunction	DXA
Sawai et al. (2018)	Interven-tional	E: n=69, mean=15 SD=0.4 C: n=79, mean=11 SD=1.4 P=0.001	endurance athletes	non-athletes	higher levels of menstrual dysfunction in endurance sports	Questionnaire

Study	**Type of Study**	**Mean, SD, Sample size, P value**	**Sports/Type**	**Control**	**Outcome Measure**	**Tests**
Nichols et al (2006)	Interven-tional	E: n=40, mean=1.14 SD=0.07 C: n=130, mean=1.17 SD=0.09 P=0.05	ALL	without menstrual ir-regularity	low bone mineral density with men-strual dys-function	DXA
Nichols et al (2006)	Interven-tional	E: n=40, mean=1.55 SD=1.6 C: n= 130, mean=1.04 SD=1.27 P=0.746	ALL	without menstrual ir-regularity	low energy availability with men-strual dys-function	Eating Disorder Exam Ques-tionnaire
Nichols et al (2006)	Interven-tional	E: n=40, mean=2.01 SD=1.3 C: n= 130, mean=1.63 SD=1.48 P=0.05	ALL	without menstrual ir-regularity	low energy availability with men-strual dys-function	Eating Disorder Exam Ques-tionnaire
Mickles-field et al. (2007)	Interven-tional	E: n=234, mean=21.6 SD=3 C: n=368, mean=21.9 SD=2.5 P=0.50	endurance athletes	BMI	higher lev-els of men-strual dys-function with low BMI	BMI

Study	Type of Study	Mean, SD, Sample size, P value	Sports/Type	Control	Outcome Measure	Tests
Barrack et al (2008)	Interven-tional	E: n=26, mean=1.11 SD=0.01 C: n=32, mean=1.07 SD=0.03 P=0.746	cross coun-try runners	no dietary restraint	low bone mineral density in those with dietary re-straint	DXA
Meng et al (2020)	Interven-tional	E: n=8, mean=1.06 SD=0.04 C: n=6, mean=1.14 SD=0.09 P=0.02	Aerobic Na-tional Teams	no dietary restraint	low bone mineral density in those with dietary re-straint	DXA
Martinsen et al (2013)	Interven-tional	E: n=28, mean=14.4 SD=4.2 C: n=156, mean=13 SD=4.4 P=0.05	endurance athletes	non-lean sports	low energy availability with lean sports	Ques-tionnaire
Klentrou et al (2003)	Interven-tional	E: N=18, mean=17.7 SD=0.4 C: N=5, mean=18.2 SD=0.5 P=0.24	gymnasts	without menstrual ir-regularity	higher lev-els of men-strual dys-function with low BMI	BMI

Study	Type of Study	Mean, SD, Sample size, P value	Sports/Type	Control	Outcome Measure	Tests
Gibbs et al (2014)	Interven-tional	E: n=187, mean=1.7 SD=2.5 C: n=250, mean=2.5 SD=1.0 P=0.746	exercising women	without menstrual ir-regularity	low bone mineral density with men-strual dys-function	ACSM criteria for bone mineral density
Dadgostar et al (2009)	Cross Sec-tional	E1: n=71, mean=9, SD=12.7 E2: n=717, mean=38 SD=5.3 P=0.05	Elite athletes	low levels of training	higher lev-els of men-strual dys-function in endurance sports	Ques-tionnaire
Cobb et al (2003)	Interven-tional	E: n=8, mean=0.97 SD=0.03 C: n=50, mean=1.02 SD=0.02 P=0.01	competitive runners	no dietary restraint	low bone mineral density in those with dietary re-straint	EDI, DXA
Cobb et al (2003)	Interven-tional	E: n=67, mean=1.1 SD=0.01 C: n=5, mean=1.07 SD=0.03 P=0.746	competitive runners	no dietary restraint	Low bone mineral density with higher levels of di-etary re-straint	EDI, DXA

Study	Type of Study	Mean, SD, Sample size, P value	Sports/Type	Control	Outcome Measure	Tests
Cialdella-Kam et al (2014)	Interven-tional	E: n=8, mean=22.3 SD=2.5 C: n=9, mean=23.2 SD=2.8 P=0.26	endurance athletes	BMI	higher lev-els of men-strual dys-function with low BMI	DXA, ExMD
Barrack et al (2010)	Cross Sec-tional	E1: n=93, mean=20.6 SD=0.3 E2: n=90, mean=22.3 SD=0.3 P=0.001	endurance athletes	non-athletes	low energy availability with lean sports	BMI
Barrack et al (2010)	Cross Sec-tional	E1: n=93, mean=10.2 SD=0.3 E2: n=90, mean=11.2 SD=0.3 P=0.02	endurance athletes	non-athletes	higher lev-els of men-strual dys-function in endurance sports	Ques-tionnaire

3.2.2 Outcome Measures

The outcome measures of this meta-analysis, as selected through the previously listed studies, were: outcome measures related to menstrual dysfunction, outcome measures related to low energy availability, and outcome measures relative to low bone mineral density.

Menstrual Dysfunction

The outcomes measures for this meta-analysis related to menstrual dysfunction were low body mass index, BMI, and high levels of training and endurance sports.

Low Energy Availability

The outcome measures for this meta-analysis related to low energy availability were lean sport participation and menstrual dysfunction.

Low Bone Mineral Density

The outcome measures for this meta-analysis related to low bone mineral density were dietary restraint, lean sport participation, and menstrual dysfunction.

3.2.3 Control Group

The effect size calculated by means of a previously developed meta-analysis software in the Excel form is an indicator of the difference between experimental and control groups, so content of control groups may affect effect size.[9] Control group participates in most studies were either non-athletes, non lean-sport high impact athletes, or athletes with criteria for the Female Athlete Triad.

3.2.4 Interventional Tests

All eighteen studies used different numbers and types of interventional tests. Studies used tests to determine BMI, questionnaires, interviews, eating disorder questionnaires, and DXA tests to determine BMI, menstrual function, energy availability, and bone mineral density.

3.3 Meta-analysis

The eighteen studies listed previously were selected for meta-analysis. In order to be included in this meta-analysis, there had to be a study/test showing a difference in the outcome measures listed above. The meta-analysis results of the eighteen studies were summarized, placed into forest plots, and presented below.

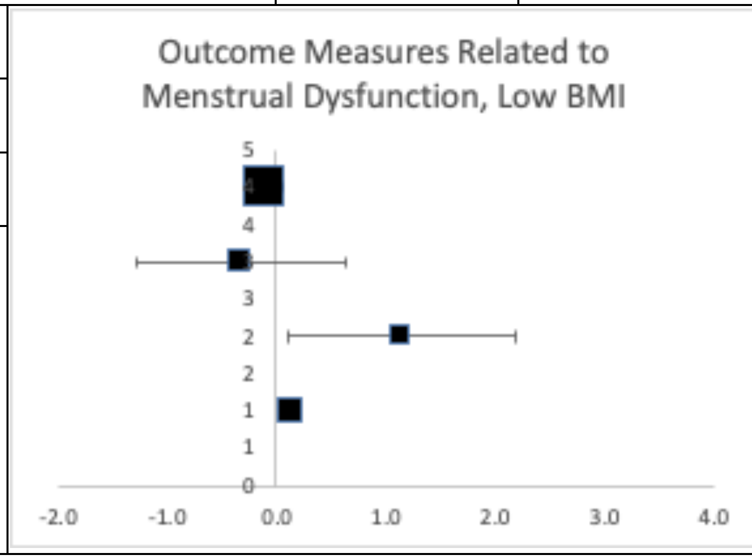
3.3.1 Outcome Measures Related to Menstrual Dysfunction

Low Body Max Index

Three trials including 642 participants found that those who had menstrual dysfunction also had lower BMI's compared to their counter-parts without menstrual dysfunction ([7, 15, 21]). Overall, there was no significant difference between experiment group and control group (95% CI, P=0.71, p>0.05), and the mean ES was 0.14, which is considered a rather small, positive ES, though not statistically significant.

Table 3.3.1 Forest Plot of LBMI

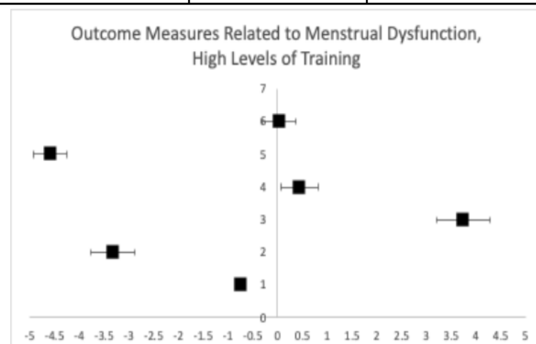
Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Micklesfield, et. al.	49.84	-.11	-.27	.05	
Cialdella-Kam, et. al.	26.22	-.32	-1.27	.64	
Klentrou, et. al.	23.94	1.14	.09	2.2	
Total	100	0.14	-0.57	0.8	
Heterogeneity and Test for Overall Effect: Q=6.04, df=2, Z=0.38, P=0.71					



High Levels of Training

Five trials including 1,454 participants tested that those who had menstrual dysfunction also participated in high levels of training/endurance training ([13, 14, 23, 27, 28]). Overall, there was no significant difference between experiment group and control group (95% CI, P=0.5920, p>0.05), and the mean ES was -0.73, which is considered a large, negative ES.

Table 3.3.2 Forest Plot of HLT

Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Vardar, et. al.	20.0	.038	-.29	.37	
Dadogostar, et. al.	20.0	-4.6	-4.9	-4.2	
Torstveit, et. al.	20.0	.453	.076	.83	
Sawai, et. al.	20.0	3.76	3.22	4.3	
Barrack, et. al.	20.0	-3.32	-3.77	-2.87	
Total	100	-0.73	-3.4	1.9	
Heterogeneity and Test for Overall Effect: Q=942.33, df=4, Z=-0.54, P=0.59					

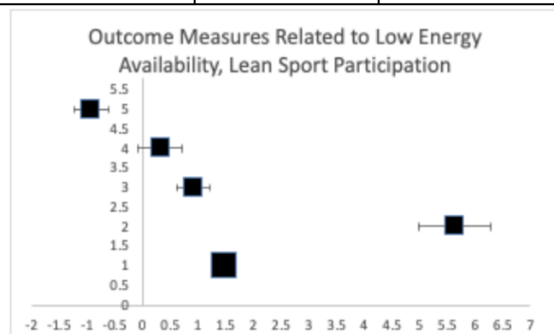
3.3.2 Outcome Measures Related to Low Energy Availability

Lean Sport Participation

Four trials including 739 participants tested that low energy availability can be caused by lean sport participation ([4, 13, 18, 27]). Overall, there was no significant difference between experimental group and control group (95% CI, P=0.15, p>.05), and the mean ES was 1.47, which is considered a large ES, though not statistically significant.

Table 3.3.3 Forest Plot of LSP

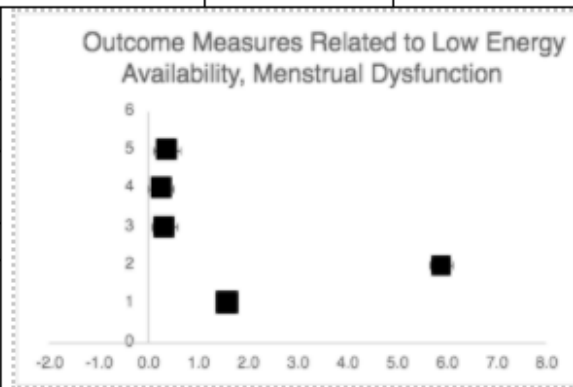
Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Torstveit, et. al.	25.0	-0.93	-1.2	-.62	
Martinsen, et. al.	25.0	0.32	-.08	.72	
Torstveit, et. al.	25.0	.93	.62	1.2	
Barrack, et. al.	25.0	5.64	4.99	6.3	
Total	100	1.47	-0.52	3.5	
Heterogeneity and Test for Overall Effect: Q=337.69, df=3, Z=1.44, P=0.15					



Menstrual Dysfunction

Four trials including 655 participants tested that low energy availability can be caused by menstrual dysfunction ([16, 22, 28]). Overall, there was a significant difference between experimental group and control group (95% CI, P=0.02, $p<0.05$), and the mean ES was 1.61, which is considered a high, statistically significant, positive ES.

Table 3.3.4 Forest Plot of MD

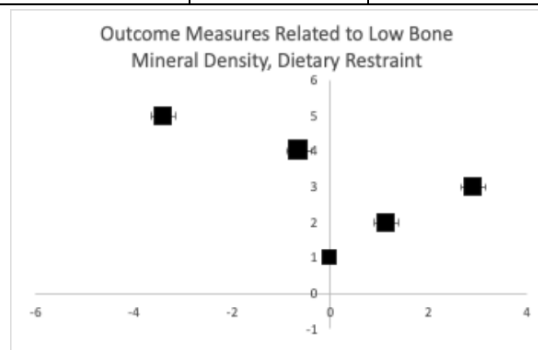
Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Nichols, et. al.	26.0	0.38	0.02	.73	
Nichols, et. al.	26.0	0.26	-0.09	.62	
Vardar, et. al.	26.0	0.34	.004	.67	
Cobb, et. al.	23.0	5.89	4.93	6.8	
Total	100	1.61	0.27	2.9	
Heterogeneity and Test for Overall Effect: Q=125.21, df=3, Z=2.36, P=0.02					

3.3.3 Outcome Measures Related to Low Bone Mineral Density

Dietary Restraint

Four trials including 581 participants tested that low bone mineral density can be caused by dietary restraint ([16, 17, 19, 20]). Overall, there was no significant difference between experimental and control groups (95% CI, P=0.9987, p>0.05), and the mean ES was .002, which is considered a small, positive ES, though not statistically significant.

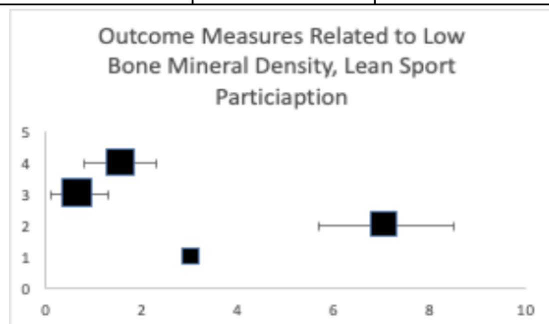
Table 3.3.5 Forest Plot of DR

Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Barrack, et. al.	25.0	-3.4	-4.48	-2.3	
Gibbs, et. al.	26.0	-0.63	-0.84	-0.4	
Cobb, et. al.	25.0	2.91	1.98	3.8	
Meng, et. al.	24.0	1.14	-0.01	2.3	
Total	100	0.02	-2.1	2.1	
Heterogeneity and Test for Overall Effect: Q=93.67, df=3, Z=0.002, P=0.99					

Lean Sport Participation

Three trials including 141 participants tested that low bone mineral density can be caused by lean sport participation/endurance training ([12, 20, 25]). Overall, there was a significant difference between experimental and control groups (95% CI, P=0.03, p>0.05), and the mean ES was 3.03, which is considered a large, statistically significant, positive ES.

Table 3.3.6 Forest Plot of LSP

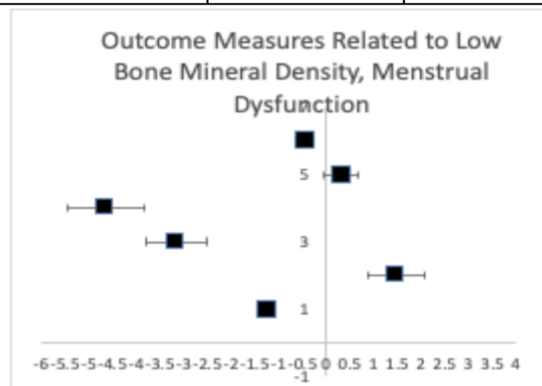
Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Tenforde, et. al.	34.0	1.56	0.82	2.3	
Valente-dos-Santos, et. al.	34.0	0.71	0.10	1.3	
Barrack, et. al.	32.0	7.09	5.68	8.5	
Total	100	3.03	0.24	5.8	
Heterogeneity and Test for Overall Effect: Q=68.97, df=2, Z=2.13, P=0.03					

Menstrual Dysfunction

Five trials including 887 participants tested that low bone mineral density can be caused by menstrual dysfunction ([16, 17, 22, 24]). Overall, there was no significant difference between experimental and control groups (95% CI, P=0.0910, p>0.05), and the mean ES was -1.25, which is considered a large, negative ES.

Table 3.3.7 Forest Plot of MD

Effect Size					Forest Plot, 95% CI
Study Author	Weight %	Random 95% CI			
		ES	Low	High	
Gibbs, et. al.	21.0	-0.44	-0.64	-0.3	
Nichols, et. al.	20.0	0.32	-0.03	0.7	
Cobb, et. al.	19.0	-4.63	-5.43	-3.8	
Cobb, et. al.	20.0	-3.15	-3.78	-2.5	
Singhal, et. al.	20.0	1.48	0.88	2.1	
Total	100	-1.25	-2.7	0.2	
Heterogeneity and Test for Overall Effect: Q=237.96, df=4, Z=-1.69, P=0.91					



Chapter 4. Discussion

Considering the combination of effect sizes and statistical significance, results from the present meta-analysis were inconclusive if menstrual dysfunction could be considered the leading clinical marker for future development of the Female Athlete Triad. Two out of the seven outcome measures were statistically significant, but only one agreed with the hypothesis of this study. The other five outcome measures did not agree with the hypothesis of this study, but were also not statistically significant.

4.1 Outcome Measures

Based on results for this meta-analysis, outcome measures were stratified into one group, with outcome measures showing statistical significance in bold. This is shown in table 4.1. Then results from this meta-analysis were discussed within different outcome measures of the Female Athlete Triad.

Table 4.1 Significance and ES of Each Outcome Measure

Outcome Measure	Significance	ES
Related to Menstrual Dysfunction; High levels of training	P=0.59, p>.05	-0.73
Related to Menstrual Dysfunction; Low BMI	P=0.71, p>.05	0.14
Related to Low Energy Availability; Lean Sport Participation	P=0.15, p>.05	1.47
Related to Low Energy Availability; Menstrual Dysfunction	P=0.02, p<.05	1.61
Related to Low Bone Mineral Density; Dietary Restraint	P=0.99, p>.05	0.02
Related to Low Bone Mineral Density; Lean Sport Participation	P=0.03, p<.05	3.03
Related to Low Bone Mineral Density; Menstrual Dysfunction	P=0.91, p>.05	-1.25

The first outcome measure shows a large, negative effect size. This shows a negative association between high levels of training leading to menstrual dysfunction, which does not agree with our hypothesis and is not statistically significant. The second outcome measure shows a small, positive effect size. This shows a positive association between low BMI leading to menstrual dysfunction, which agrees with our hypothesis although not statistically significant. The third outcome measure shows a large, positive effect size. This shows a positive association between lean sport participation leading to low energy availability, which does not agree with our hypothesis and is not statistically significant. The fourth outcome measure shows a large, positive effect size. This shows a positive association between menstrual dysfunction leading to low energy availability, which agrees with our hypothesis and is statistically significant. The fifth outcome measure shows a small, positive effect size. This shows a positive association between dietary restraint leading to low bone mineral density, which agrees with our hypothesis although not statistically significant. The sixth outcome measure shows a large, positive effect size. This shows a positive association between lean sport participation leading to low bone mineral density, which does not agree with our hypothesis although it is statistically significant. The seventh outcome measure shows a large, negative effect size. This shows a negative association between menstrual dysfunction leading to low bone mineral density, which does not agree with our hypothesis and is not statistically significant.

4.1.1 Menstrual Dysfunction

The first two outcome measures were related to menstrual dysfunction—low body mass index and high levels of training. These two have been shown through past research to have significant effects on menstrual dysfunction ([7, 13, 14, 15, 21, 23]). Results from this meta-analysis showed that low body mass index and high levels of training did not demonstrate statistical significance to the development of menstrual dysfunction in the female athlete. Low body mass index showed a small, positive effect size, which was not statistically significant, and high levels of training showed a large, negative effect size, which was also not statistically significant. In this meta-analysis, low body mass index did not show significant association with the Triad as its P value was not statistically significant, even though it did have a small, positive ES and association. There was a slight positive trend noted on the forest plot for low body mass index. Low BMI for menstrual dysfunction agrees with the hypothesis as there was a small, positive association. This was expected to be the case due to past research, and it was expected to be a small association. In this meta-analysis, high levels of training showed a large, negative ES, which shows an association with the Triad opposite of what was expected; it was also not statistically significant. There was no trend noted on the forest plot for high levels of training. High levels of training had a null result, as the proposed expectation was the it would show a small, positive association with menstrual dysfunction. In order to verify the true effect of low body mass index and high levels of training on menstrual dysfunction, more data is necessary. Therefore, these two outcome measures did not support the hypothesis as neither were statistically significant.

4.1.2 Low Energy Availability

The second two outcome measures were related to low energy availability—lean sport participation and menstrual dysfunction. These two have been shown in the past to have significant effect on the development of low energy availability ([4, 13, 16, 18, 22, 28]). Results from this meta-analysis showed that lean sport participation did not demonstrate statistical significance in the development of low energy availability in the female athlete, but that menstrual dysfunction did. In this meta-analysis, lean sport participation showed a large, positive effect size, which shows an association with the Triad opposite of what was expected; however, it was not statistically significant. There was a negative trend noted on the forest plot for lean sport participation related to low energy availability. Lean sport participation had a null result, as the proposed expectation was that it would show a small, positive association with energy availability. In order to verify the true effect of lean sport participation on low energy availability, more data is necessary. Menstrual dysfunction showed a large, positive ES, which shows an association with the Triad as expected; and it was statistically significant. There was a slight positive trend noted on the forest plot for menstrual dysfunction related to low energy availability. Menstrual dysfunction agreed with the hypothesis as there was a large, positive association. Therefore, the outcome measure of lean sport participation did not support our hypothesis, but the outcome measure of menstrual dysfunction did, as it showed an association between menstrual dysfunction on the rest of the Triad.

4.1.3 Low Bone Mineral Density

The final three outcome measures were related to low bone mineral density—dietary restraint, lean sport participation, and menstrual dysfunction. All three have been shown through past studies to have a significant effect on bone mineral density in the female athlete ([12, 16, 17, 19, 20, 22, 24, 25]). Results from this meta-analysis showed that dietary restraint and menstrual dysfunction did not demonstrate statistical significance in the development of low bone mineral density, but that lean sport participation did. In this meta-analysis, dietary restraint showed a small, positive ES, which shows an association with the Triad as expected; however, it was not statistically significant. There was not a trend noted on the forest plot for dietary restraint related to low bone mineral density. Dietary restraint agreed with the hypothesis as there was a small, positive association, and it was expected to be a small association. Menstrual dysfunction showed a large, negative ES, which showed an association with the Triad opposite of what was expected; it was also not statistically significant. There was a negative trend noted on the forest plot for menstrual dysfunction related to low bone mineral density. Menstrual dysfunction had a null result, as the proposed expectation was that menstrual dysfunction would show a large, positive association. Lean sport participation showed a large, positive ES, which showed an association with the Triad opposite of what was expected; it was statistically significant. There was a positive trend noted on the forest plot for lean sport participation related to low bone mineral density. Lean sport participation had a null result, as the proposed expectation was that it would show a small, positive association with bone mineral density. Therefore, the three outcome measures of low bone mineral density did not support the hypothesis, as two were not statistically significant, and one did not agree with the hypothesis.

4.1.4 Relationship Between Menstrual Dysfunction, Low Energy Availability, and Low Bone Mineral Density

The three components of the Female Athlete Triad displayed through their outcome measures in this meta-analysis showed their relationships in a new way. We know from previous research that the Triad is a continuum, and each component of the Triad has a high likelihood of causing the other components to occur in a female athlete as well[1]. Through our seven outcome measures in this meta-analysis, we attempted to show an association of menstrual dysfunction as the main perpetuator of the rest of the components of the Triad. Although our hypothesis was not supported, there is still evidence in this study about the effects of menstrual dysfunction on the rest of the Triad. All of our outcome measures that we expected to show positive association between menstrual dysfunction on the rest of the Triad did, however were not statistically significant. If we had had more studies and cases included in this meta-analysis, there is a very good chance that our hypothesis would have been supported. Menstrual dysfunction greatly effects energy availability and bone mineral density, as it can be easily ignored in young female athletes and estrogen has such a significant influence on bone, energy and nutrient absorption.

4.1.5 The Significance of the Results in Clinical Practice

The significance of this meta-analysis is applicable to clinical practice for healthcare professionals. Three out of seven of the outcome measures agrees with the hypothesis, although only one was statistically significant. However, this meta-analysis was able to show the interactions that menstrual dysfunction has on the other members of the Triad. In past clinical resources, eating disorders or low energy availability has been highlighted as the first component of the Triad that will appear in a female athlete. We have seen that that is simply not the case. There are many different outcome measures that can perpetuate the development of the Triad, and this meta-analysis highlights seven of them. Healthcare professionals, athletic coaches, and parents need to be made aware of the evolving clinical markers for the development of the Triad if we are to successfully limit future diagnoses. Special consideration should be placed on awareness and education of the effects of menstrual dysfunction on the female athlete, as menstrual dysfunction can easily go untreated for long periods of time causing innumerable damages.

4.2 Central Hypothesis

The central hypothesis of this meta-analysis was that menstrual dysfunction in the female athlete could be the leading cause of and could perpetuate or trigger the development of the Triad as a whole. The first part of this hypothesis was based on the effects that menstrual dysfunction has on bone mineral health and energy availability, compared to other outcome measures that affect bone mineral health and energy availability. The one outcome measure that showed a high positive association between the effects of menstrual dysfunction on the rest of the Triad was statistically significant, the outcome measure of menstrual dysfunction related to low energy availability. This did support our hypothesis. The second part of this hypothesis was based on the effects of the other Triad components on menstrual dysfunction. The one outcome measure that showed a moderate positive association between a non-Triad component and menstrual dysfunction was not statistically significant. However, the other statistically significant outcome measures were the effects of lean sport participation on bone mineral density, which did not support our hypothesis. All other outcome measures either did not show a positive, statistically significant association between the effects of menstrual dysfunction on the rest of the Triad, or showed a positive association between other Triad components on each other. Therefore, our hypothesis was not supported, despite one outcome measure supporting it. Unfortunately, in this study, we had occurrences of negative associations that were not expected. Two out of our seven outcome measures showed negative associations, where we expected all of them to show positive associations. This contributed to the less-favorable results of the study because there was cancellation between the positive associations and the negative ones. We are unable to make definitive claims about the results of this study; one, because the majority of the outcome measures were not statistically significant, and two, because the negative correlations cancelled out some of the positive ones. To summarize, results from this meta-analysis did not support menstrual dysfunction being the leading clinical marker for future development of the Female Athlete Triad, although future studies are warranted.

4.3 Conclusions

4.3.1 Other Clinical Markers of the Female Athlete Triad

Despite the hypothesis of this meta-analysis not being supported, there are still conclusions that can be made from it. Through the research and outcome measures found, there is a wide variety of other potential clinical markers that were found. Low BMI, lean sport participation, dietary restraint, and high levels of training were all found to be clinical markers of the components of the Female Athlete Triad. If researchers and healthcare providers can acknowledge these and do future studies on these components as well as others, there can still be the benefits that this study was hoping to provide through this initiative summative meta-analysis in the Female Athlete Triad.

4.3.2 The Components of the Female Athlete Triad

This study attempted to explore the association of individual components of the female athlete triad with the risk factors for the future development of the triad. Despite the overall outcome measures not being statistically significant, there is still evidence of the individual components perpetuating the diagnosis of the Triad in the future.

4.4 Limitations

This meta-analysis has limitations, due to limited data and variance between studies. The outcome measures in this study were limited to only seven. There are many more outcome measures that are related to the components of the Female Athlete Triad that were unable to be included in this study. There are also many variables that could affect the components of the

Triad that are impossible to include in this study; for example: the effects of contraception on menstrual dysfunction, the effects of environment on eating disorders, and the effects of genetics on bone mineral density.

In order to investigate these variables, more studies and detailed information are needed to be completed. Since this meta-analysis overlooked these variables, generalized different studies, and combined study findings together, the results from this study were limited. There is a wide number of future studies that could be done on this topic, and the important clinical markers of the Female Athlete Triad.

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