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2	Amenorrhea and oligomenorrhea risk related to exercise training volume and intensity: Findings from
3	3,705 participants recruited via the STRAVA <sup>™</sup> exercise application
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## 27 Abstract

28 The physiological underpinnings of amenorrhea/oligomenorrhea (AO) among exercising women 29 are complex and incompletely understood. Objectives: To investigate associations between self-reported 30 exercise training habits and AO among physically active women. Design: A cross-sectional survey was 31 completed by 3,705 women (median age = 40 years [Quartile 1, Quartile 3: 30, 45], body mass index [BMI] = 22.1 kg/m<sup>2</sup> [20.5, 24.2]) representing multiple nationalities and sports via the STRAVA<sup>TM</sup> exercise 32 application. Respondents selected the amount of time they participated in low intensity (LIT), moderate 33 34 intensity (MIT), and high intensity training (HIT) per week. Method: Associations between weekly 35 volumes of LIT, MIT, and HIT and AO were assessed with univariate logistic regression models, followed 36 by models adjusted for age and BMI. Results: AO prevalence was 16% (n = 576/3,705) and was not 37 associated with country of origin or most sport modes assessed. In adjusted models, LIT  $\geq$  7 h/week and 38 MIT  $\ge 6$  h/week was associated with a 1.43 (95% CI:1.04 - 1.96, p = 0.03) and 1.46 (1.10 - 1.95, p = 0.01) 39 greater risk for AO, respectively, compared to 2 to 3 h/week. Participating in LIT for  $\leq$  30 min/week 40 compared to 2 to 3 h/week was associated with reduced AO risk (0.65 [95% CI: 0.44 - 0.94, p = 0.02]). HIT 41  $\geq$  5 h/week was associated with a 1.41 (1.03 - 1.92, p = 0.03) greater AO risk compared to 1 to 2 h/week. 42 **Conclusions:** Collectively, these associations suggest that greater weekly exercise volumes, irrespective of 43 intensity, may increase AO risk. 44 45 46

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50 KEYWORDS: RED-S, female athlete triad, menstrual cycle, sports

### 53 Introduction

54 Menstrual cycle dysfunction, which includes the infrequency or complete absence of menses [i.e., 55 amenorrhea and oligomenorrhea (AO)], has been estimated to affect up to 60% of women who regularly exercise compared to <11% of sedentary women.<sup>1-3</sup> The physiological underpinnings of AO are complex 56 57 and incompletely understood, but have been attributed to low energy availability with resultant hypothalamic-pituitary-gonadal axis dysfunction and subsequent suppression of ovarian sex hormone 58 production <sup>4-6</sup>. Even when energy balance is well maintained during periods of intensified physical training, 59 60 there is some evidence suggesting the stress of exercise itself may increase AO risk. For example, despite 61 demonstrating a linear increase in the frequency of menstrual cycle dysfunction with greater magnitudes of 62 energy deficiency attained through a controlled diet and exercise intervention, Williams et al. (2015) 63 observed 1/8 (13%) women developed oligomenorrhea in a control group where energy balance was maintained (+80 Kcal/day).<sup>7</sup> Lieberman et al. (2018) also found estrone-1-glucuronide, pregnanediol 64 65 glucuronide, and luteinizing hormone excretion was suppressed following the initiation of a ~3 month exercise training intervention in untrained women independent of energy availability.<sup>8</sup> Collectively, these 66 67 findings suggest the stress of habitual exercise may increase AO risk regardless of energy availability.

68 Current clinical guidance for reversing AO includes facilitating energy balance through reductions in exercise training and/or increasing caloric intake.<sup>4-6</sup> Specifically, in regards to exercise training, it is 69 70 unclear whether modifications in usual volume or intensity should be prioritized in reducing AO risk and 71 data is lacking to make such recommendations. For example, previous work relating intensified physical 72 training to increased AO frequency have either implemented exercise programs in untrained women which necessitates an increase in usual activity volume and intensity,<sup>7-10</sup> or have made associations with training 73 74 volume without accounting for possible differences in intensity.<sup>11, 12</sup> Identifying whether certain modifiable 75 exercise training characteristics, such as volume and/or intensity, are related to AO risk would improve its 76 management and prevention. Importantly, chronic ovarian suppression with AO is linked to a host of longterm health consequences such as low bone mineral density and cardiovascular disease.<sup>5</sup> Accordingly, the 77

#### 82 Methods

83 An electronic cross-sectional survey localized to 7 countries (United Kingdom, Republic of Ireland, United States of America, France, Spain, Italy, and Germany) was sent to 425,697 women aged  $\geq 18$  years 84 who were members of a web-based exercise activity tracking service, STRAVA™. The survey was 85 86 administered via email or hyperlink visible on the STRAVA<sup>™</sup> mobile application and was available for 25 87 days from 14 February 2019 to 11 March 2019. Of those invited, 16,423 (3.9%) women started the survey 88 and 10,371 (2.4%) completed it in its entirety. Additional details of survey design and administration have been published previously.<sup>13</sup> Survey protocol was approved by the Ethics Committee of St. Mary's 89 90 University (SMEC 2018-19 011), Twickenham, UK and informed consent was obtained prior to 91 participants providing responses.

Participants were asked to retrospectively recall how many periods they had in the last year and
were given options to select "0-3," "4-6," "7-10," "11-13," "14-16," "17-19," or "19+." AO was defined as
reporting 0-10 periods, eumenorrhea as 11-16 periods, and polymenorrhea as ≥17 periods annually.
Categories for menstrual cycle status were based on previously published characteristics of 612,613 women,
in which 92% reported menstrual cycle intervals between 21 to 35 days.<sup>14</sup> A regular 21-35 day menstrual
cycle results in approximately 11-17 periods per year.

98 Participants were also asked to select which exercise modalities they regularly participated in at 99 least once per week (Table 1). Weekly exercise volume was quantified by asking participants to recall how 100 much time they usually spent per week doing high intensity training (HIT; "hard and fast breathing, can't 101 hold a conversation"), moderate intensity training (MIT; "hard breathing, can hold a conversation"), or low 102 intensity training (LIT; "easy breathing") over the last month with the option to select "none," "0-30 103 minutes," "30 minutes-1 hour," "1-2 hours," "2-3 hours," "3-4 hours," "4-5 hours," "5-6 hours," "6-7
104 hours," "7-8 hours," "8-9 hours," "9-10 hours," or "10+ hours."

105 Only participants with complete survey responses were included in the present analyses (n =106 10,371); from which 6,666 (64.3%) were excluded for the following reasons: reporting never having had a 107 period (primary amenorrhea); currently pregnant / breastfeeding / started going through menopause / 108 menopausal in the last year; diagnosed with polycystic ovary syndrome / endometriosis / premature ovarian failure / excess prolactin production / endometrial polyps or fibroids / adenomyosis / pelvic inflammatory 109 110 disorder / cancers affecting the uterus or cervix; currently using hormonal contraceptives including implants 111 / injections / hormonal intrauterine devices / vaginal rings / oral contraceptive pills / oestrogen patches / 112 hormonal replacement therapies; or had a hysterectomy. Additionally, those identified as extreme outliers 113 for body mass index (BMI) or age (3\*interquartile range [IQR]) were removed along with those who 114 reported having  $\geq 17$  menstrual cycles in the last year (polymenorrhea). A total of 3,705 (35.7%) women 115 were included in final analyses.

116 Chi-square tests were used to evaluate associations between AO risk and categorical variables 117 (country, sport). Group differences between AO vs. eumenorrheic participants for age and BMI were 118 assessed using Mann Whitney U-tests as continuous variables were non-normally distributed. Logistic 119 regressions assessed associations between LIT, MIT, and HIT volume categories and AO risk in univariate 120 models, followed by models adjusted for age and BMI. Categories with the most frequent responses for LIT 121 (2 to 3 h; 20.8% [772/3.705] of responses), MIT (2 to 3 h; 22.5% [835/3.705] of responses), and HIT (1 to 122 2 h; 22.9% [850/ 3,705] of responses) were selected as reference categories. Remaining categories were 123 collapsed such that each category constituted >10% of responses. Statistical significance was set at p < 0.05. 124 All statistical comparisons were made using SPSS (v.27.0) software.

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### 126 Results

127Demographic information for the included sample (n = 3,705) along with prevalence for AO (n =128576; 16%) or eumenorrhea (n = 3,129; 84%) based on age, BMI, country, and sport are provided in Table

129 1. AO women were younger and had a lower BMI compared to the eumenorrheic group. AO was not 130 associated with country of origin or most exercise modes reported. However, women who participated in 131 dance class/dance-based fitness classes were more likely to have AO than women who did not participate 132 in dance despite having similar BMI (p = 0.16) and age (p = 0.21).

Table 2 displays unadjusted and adjusted odds ratios with 95% confidence intervals for AO risk based on weekly LIT, MIT, and HIT volume categories. Compared to 2 to 3 h/week of LIT, participating in  $\geq 7$  h/week of LIT was associated with increased AO risk while participating in  $\leq 30$  min/week of LIT was associated with decreased risk of AO. Similarly, participating in  $\geq 6$  h/week of MIT or  $\geq 5$  h/week of HIT was associated with increased risk of AO compared to 2 to 3 h/week of MIT and 1 to 2 h/week of HIT, respectively.

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## 140 Discussion

In our analyses of 3,705 women representing multiple nationalities and sports, 16% (n = 574) reported AO, i.e., infrequent ( $\leq 10$  menstrual cycles) or no menses in the last year. Weekly exercise volume above a certain threshold increased AO risk, regardless of the intensity it was performed. For example, women who reported LIT volumes  $\geq 7$  h/wk, MIT volumes  $\geq 6$  h/wk, or HIT volumes  $\geq 5$  h/wk compared to 2 to 3 h/wk for LIT and MIT and 1 to 2 h/wk for HIT had a ~40% greater risk of AO. Collectively, these associations suggest that excessive weekly exercise volume, of any intensity, may increase odds of developing AO among physically active women.

A comprehensive understanding of factors contributing to the greater prevalence of AO among exercising women remains elusive; however, intensified exercise training has been theorized to increase AO risk.<sup>4, 15, 16</sup> Initial work corresponding to the influx of women competing in endurance events such as the marathon during the 1980's attributed higher training volumes and/or intensity to the greater prevalence of AO observed among certain female athletes. For example, frequency of amenorrhea was shown to positively correlate with weekly mileage in runners, <sup>11, 12</sup> but possible differences in intensity of training between runners completing fewer vs. more miles per week was not considered. Russell et al. (1984) also observed (unspecified) reductions in training to result in resumption of normal menses among oligomenorrheic clublevel swimmers practicing 25 hours/week.<sup>17</sup> Further accounts supported increases in the frequency of menstrual cycle dysfunction with initiation of controlled exercise training interventions, but were conducted in untrained women and as such involved increases in the volume and intensity of usual activity.<sup>9, 10</sup> While the conclusions of these earlier studies generally support periods of intensive physical training contribute to greater AO frequency in physically active women, they do little to clarify whether AO risk is modified by certain specific training characteristics, such as exercise volume or intensity.

162 One of our primary findings is the association between exercise volume and increased risk of AO, 163 irrespective of exercise intensity. We found AO risk to be elevated to a similar extent for women reporting 164 LIT, MIT, and HIT volumes comprising the top 10-16% of responses. The increase in AO risk among 165 women who report relatively high weekly exercise volumes may plausibly be related to greater exercise 166 energy expenditure and increased likelihood of low energy availability with longer duration training 167 sessions. Additionally, greater exercise volume might also indicate a higher frequency of training sessions 168 performed per week, which due to the anorexigenic effect of acute exercise that lasts for several hours, could result in an inadequate intake of calories to match energy expenditure between subsequent bouts <sup>18</sup>. Previous 169 170 work has shown that the risk of low energy availability increases for every hour of exercise per week, but is not dependent on intensity of sport among recreational exercisers <sup>19</sup>. As such, increased risk of AO with 171 172 greater exercise volume may be attributed to a higher likelihood of low energy availability with due to 173 exercise energy expenditure uncompensated for by diet rather than the stress of exercise itself. Findings 174 from Loucks et al. (1998) demonstrating no disruptive effects of 4 days of exercise energy expenditure equivalent to 30 Kcal/ kg lean body mass/ day when energy intake is matched provide support for this 175 theory.<sup>20</sup> However, additional controlled interventions held over a longer duration are needed to determine 176 177 whether habitually elevated exercise volume negatively influences AO risk independent of energy 178 availability.

179 Interestingly, reporting LIT volumes ≤ 30 min/week was associated with reduced AO risk compared
180 to 2 to 3 h/week while similar associations were not observed for MIT or HIT. Greater volumes of LIT may

181 reflect exercise sessions that are non-specific to competitive training objectives, such as adding in "junk 182 miles" or cross-training sessions for the purpose of increasing caloric expenditure rather than improving 183 fitness or a specific sports skill. In support of this theory, Tomten et al. (1996) found long-distance runners 184 with regular and irregular menstrual cycles to practice similar amounts of HIT (sessions >85% maximum heart rate), while women with irregular cycles engaged in more LIT (sessions <85% maximum heart rate).<sup>21</sup> 185 186 Ravi et al. (2021) also observed higher daily step counts despite similar reported sport-specific volumes 187 among AO versus eumenorrheic Finnish athletes, with a difference of  $\sim$  5,000 steps per day between groups.<sup>1</sup> 188 As such, the reduced AO risk we observed for women reporting the lowest amounts of LIT per week may 189 be reflective of differences in exercise session intention and susceptibility to low energy availability.

190 Our finding that AO risk was not increased to a greater extent with HIT vs. LIT or MIT contradicts 191 previous evidence suggesting higher training intensities have a suppressive effect on ovarian sex hormone 192 production. The stimulatory effects of *acute* high-intensity exercise on  $\beta$ -endorphin<sup>22</sup> or glucocorticoid release<sup>23</sup> have been cited as reasons for AO in women undergoing intensive exercise training due to 193 interaction with the hypothalamic-pituitary-adrenal axis and suppression of luteinizing hormone.<sup>17</sup> 194 195 However, some evidence suggests chronic strenuous exercise training lowers basal plasma β-endorphin concentrations,<sup>24</sup> and blunts the rise in plasma  $\beta$ -endorphin and glucocorticoid release<sup>25</sup> experienced with 196 197 acute high-intensity exercise. Such adaptions oppose the heightened endocrine response to exercise stress observed in women with AO.<sup>26</sup> As such, exercise intensity per se, may not increase AO risk. 198

199 Furthermore, previous evidence suggests that HIT, only when combined with low energy 200 availability, may result in AO. For example, 4 days of performing high-intensity (70% maximal aerobic 201 capacity) and high-volume (~3 hours/ day) exercise with low energy availability has been shown to disrupt luteinizing hormone pulsatility.<sup>20</sup> Whereas, the same exercise intervention did not have an effect on 202 luteinizing hormone when energy expenditure was balanced with energy intake.<sup>20</sup> Performing more HIT has 203 also been linked to improved BMI and fat free mass index in anorexia nervosa patients,<sup>27</sup> and it has been 204 205 suggested that HIT may increase ad libitum caloric intake to a greater extent than LIT in the meal directly following exercise in recreationally active women.<sup>28</sup> These energy balancing effects might be attributed 206

207 more to a psychological (i.e., self-granted "allowance" to eat more after a training session that is deemed as 208 strenuous vs. non-strenuous) versus physiological response as there is inconsistency in the literature and a 209 paucity of data collected in women to support the effects of exercise intensity on appetite.<sup>27, 29</sup> Accordingly, 210 as our findings support, modifications in exercise volume rather than session intensity may have a greater 211 influence on AO risk.

212 The relatively low prevalence of AO reported in our sample compared to other previous accounts 213 could be attributed to the median age of participants (40 years [Quartile 1, Quartile 3: 30, 45]) as previous 214 work has demonstrated greater resiliency against reductions in luteinizing hormone with low energy availability attained through diet and exercise intervention in women as gynecological age advances.<sup>30</sup> 215 216 Alternatively, it could be attributed to the wide-range of competitive levels (i.e., recreational to professional 217 athletes) and sport types of exercisers who use the STRAVA<sup>™</sup> exercise application. The diversity of sport 218 type and ability level along with the multinational representation of survey respondents is also a strength of 219 our investigation. Our sample represents a group of physically active women who were users of the STRAVA<sup>™</sup> exercise application, and therefore their exercise and diet habits likely differ from a more 220 221 general population. Notably, the majority of our sample met minimum moderate to vigorous physical 222 activity recommendations of  $\geq$  150-300 min/week of moderate or  $\geq$  75-150 min/week of vigorous aerobic 223 activity or an equivalent combination of moderate and vigorous activity (n = 3168; 86%).

224 The self-report mode of assessment and necessity of survey participants to have access to 225 technology are identifiable limitations of our analyses. While self-report surveys facilitate greater 226 participation, recall bias is possible, and we cannot exclude the possibility of recall or social desirability 227 biases. To minimize the latter, only participants with complete survey responses were included and those 228 who were identified as extreme outliers for age and BMI were removed. Nevertheless, conclusions of this 229 research should be confirmed by more controlled, objective measures (i.e., accelerometry, hormonal 230 confirmation of AO). Further, as this survey was administered cross-sectionally, additional work is needed 231 to establish how changes in exercise volume and intensity may longitudinally influence AO risk.

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233	Concl	usion

Our analyses of 3,705 women representing multiple nationalities and sports suggest AO risk is influenced by greater exercise training volume, irrespective of intensity. Women reporting LIT, MIT, or HIT volumes comprising the top 10-16% of responses had a ~40% increased risk of AO. Collectively, these findings indicate certain habitual exercise training characteristics, such as weekly volume, should be considered in the management of AO among physically active women.

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## 240 Practical Implications

- Our primary findings suggest that women who participate in relatively high weekly volumes of
   exercise, regardless of the intensity at which exercise sessions are performed, are at an increased
   risk for irregular or missed periods.
- Participating in minimal amounts of low intensity training (≤ 30 min/week) may be a strategy to
   decrease the risk for irregular or missed periods.
- Practitioners should consider assessing exercise volume as a risk factor for irregular or missed
   periods among physically active women.
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# 252 Declarations of Interest

- 253 M.N.B., S.J.C., and J.M.B. have no competing interests to declare. G.B., C.R.P., and J.A.F., are employees
- 254 or consultants for Orreco and creators of the FitrWoman application.
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### 256 Data Availability

- 257 Data underpinning these analyses are available from the authors upon request.
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	Total Sample	AO	Eumenorrheic	p-value
	n = 3,705	n = 576	n = 3,129	
		(16%)	(84%)	
Age (years), median (Q1 - Q3)	40	35	40	< 0.01*
	(30 - 45)	(25 - 35)	(30 - 45)	
<b>BMI (kg/m<sup>2</sup>),</b> median (Q1 - Q3)	22.1	21.4	22.2	<0.01*
	(20.5 – 24.2)	(20.0 - 23.5)	(20.6 - 24.4)	
Country n (%)				0.70
Brazil	384 (10)	50 (13)	334 (87)	
France	652 (18)	97 (15)	555 (85)	
Germany	489 (13)	79 (16)	410 (84)	
Spain	540 (15)	91 (17)	449 (83)	
UK	761 (21)	119 (16)	642 (84)	
USA	879 (24)	140 (16)	739 (84)	
Sport n (%)				
Running	2860 (77)	447 (16)	2413 (84)	0.80
Cycling	1571 (42)	244 (16)	1327 (84)	0.98
Weight Training	1265 (34)	213 (17)	1052 (83)	0.12
Gym Based Classes	1009 (27)	159 (16)	850 (84)	0.83
Other Prolonged Exercise	684 (19)	110 (16)	574 (84)	0.67
Swimming	638 (17)	113 (18)	525 (82)	0.10
Cross Trainer	424 (11)	79 (18)	345 (81)	0.06
Dance Class	206 (6)	45 (22)	161 (78)	0.01*

**351** Table 1. Descriptive information for the sample meeting inclusion criteria (n = 3,705) and for women

	Team Sports	156 (4)	29 (19)	127 (81)	0.28
	Racquet Sports	96 (3)	13 (14)	83 (86)	0.58
	Martial Arts	52 (1)	6 (12)	46 (88)	0.42
353	$\overline{AO} = amenorrhoeic / oligometers$	enorrheic. BMI = body mass	s index. UK = Uni	ted Kingdom / Ire	land. USA =
354	United States of America. Q1=	= quartile 1. Q3= quartile 3.	* $p < 0.05$ between	AO and eumenor	rheic groups.
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		n (%)	Unadjusted OR	р-	Adjusted OR	р-
			(95% CI)	value	(95% CI)	value
LIT						
	$\leq$ 30 min	416 (11)	0.64 (0.44 - 0.92)	0.02*	0.65 (0.44 - 0.94)	0.02*
	30 min to 1 h	410 (11)	1.12 (0.81 - 1.56)	0.48	1.14 (0.82 – 1.58)	0.45
	1 to 2 h	672 (18)	1.06 (0.80 – 1.41)	0.69	1.05 (0.79 – 1.41)	0.72
	2 to 3 h	772 (21)	Ref.		Ref.	
	3 to 4 h	450 (12)	1.20 (0.88 - 1.65)	0.25	1.20 (0.87 – 1.64)	0.27
	4 to 7 h	605 (16)	0.92 (0.68 - 1.25)	0.61	0.91 (0.67 – 1.24)	0.55
	$\ge 7 h$	380 (10)	1.51 (1.10 – 2.07)	0.01*	1.43 (1.04 – 1.96)	0.03*
MIT						
	$\leq 1 h$	431 (12)	1.09 (0.79 – 1.51)	0.61	1.13 (0.81 – 1.58)	0.47
	1 to 2 h	630 (17)	0.87 (0.64 – 1.18)	0.36	0.85 (0.63 - 1.16)	0.32
	2 to 3 h	835 (23)	Ref.		Ref.	
	3 to 4 h	613 (17)	1.23 (0.92 – 1.64)	0.17	1.20 (0.90 – 1.61)	0.21
	4 to 6 h	615 (17)	1.24 (0.93 – 1.65)	0.15	1.17 (0.88 – 1.57)	0.28
	$\geq 6 h$	581 (16)	1.45 (1.09 – 1.93)	0.01*	1.46 (1.10 – 1.95)	0.01*
HIT						
	$\leq$ 30 min	405 (11)	1.16 (0.84 – 1.61)	0.37	1.26 (0.91 – 1.78)	0.17
	30 min to 1 h	706 (19)	0.82 (0.61 – 1.10)	0.18	0.84 (0.62 – 1.13)	0.24
	1 to 2 h	850 (23)	Ref.		Ref.	
	2 to 3 h	707 (19)	1.11 (0.84 – 1.47)	0.46	1.08 (0.81 - 1.43)	0.59
	3 to 5 h	609 (16)	1.30 (0.98 – 1.73)	0.07	1.28 (0.96 – 1.70)	0.10
	$\geq 5 h$	428 (12)	1.44 (1.06 – 1.95)	0.02*	1.41 (1.03 – 1.92)	0.03*

OR = odds ratio unadjusted and adjusted for age and BMI. Ref. = reference category. LIT = low intensity
training. MIT = moderate intensity training. HIT = high intensity training. \*p < 0.05 between AO and</li>
eumenorrheic groups.