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Physical Conditioning, Obesity and Fibromyalgia: Causal Relationship or Confounding?

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Fibromyalgia syndrome (FMS) constitutes a significant public health concern due to its substantial global prevalence estimate (approximately 4%, predominantly affecting women), resulting in a considerable mental and physical burden, as well as high economic costs (D'Onghia et al., 2022). It encompasses a wide spectrum of clinical manifestations, including widespread pain, hypersensitivity, fatigue, depression, cognitive impairment, and sleep disturbance. These symptoms may prove refractory to prescribed medications and combined therapy strategies. The multifaceted and complex nature of these symptoms makes it challenging to comprehend the underlying etiology and physiopathology, thereby hindering accurate diagnosis and treatment. Nevertheless, several pathophysiological explanations have been proposed, including central sensitization, impairment of the endogenous pain inhibitory system, systemic inflammation, neurotransmitter system imbalance, and peripheral neuropathy, with some overlap among these hypotheses (Siracusa et al., 2021). Given the significance of FMS and the current gaps in understanding its mechanisms, it is crucial to further investigate clinically relevant factors associated with this syndrome, two of which are physical conditioning and obesity.

Physical conditioning refers to the capacity to sustain short- or long-term activities without experiencing excessive fatigue and is dependent on a good level of physical fitness and its components, including muscle strength and endurance, cardiorespiratory capacity, flexibility, etc. There is an interesting relationship between physical conditioning and FMS. Studies have demonstrated that higher levels of physical fitness are associated with lower FMS severity (Soriano-Maldonado et al., 2015). Additionally, women with FMS have shown reduced tolerance to exercise compared to healthy women matched by age, body mass index (BMI), and physical activity level (Tavares et al., 2020; Merriwether et al., 2018).

The reduced tolerance to exercise combined with fatigue could contribute to the low levels of physical activity and high levels of inactivity and sedentary behavior reported in FMS (Vancampfort et al., 2023a, 2023b). Notably, an independently strong association between physical conditioning and a higher risk of developing this syndrome has not been reported. However, similar to other chronic conditions, maintaining good physical condition may contribute to better health. Evidence suggests that regular exercise may help improve sleep, as well as alleviate anxiety, depression, and fatigue (Busch et al., 2007; Izquierdo-Alventosa et al., 2020). International guidelines strongly recommend physical training, primarily in the form of aerobic exercise and strengthening as part of a comprehensive treatment plan targeting chronic pain, physical function, and overall well-being in FMS (Macfarlane et al., 2017; Vilarino et al., 2023).

Overweight and obesity, as measured through BMI, exhibit a direct relationship with FMS, raising important questions about the nature of this relationship in terms of etiology and pathophysiology. Obese patients with FMS experience higher levels of disability, more depressive symptoms, and an increased burden

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of comorbidities. The severity of FMS is positively correlated with BMI, with higher BMI levels associated with greater disability and symptom severity (Arranz et al., 2012; Atzeni et al., 2021). The prevalence of FMS in obese individuals, as reported in two cohorts, ranges from 37% to 51%, significantly surpassing the estimate for the general population (Heidari et al., 2017). Longitudinal studies have indicated that overweight and obese women face a higher risk of developing FMS compared to their normal-weight counterparts. This risk is further elevated for those who reported lower levels of physical activity at baseline (Mork et al., 2010; Markkula et al., 2016). Particularly, obesity has been associated with other rheumatological conditions such as osteoarthritis in both weight-bearing and non-weight-bearing joints, suggesting shared pain-related mechanisms beyond excessive mechanical overload on the joints (Ursini et al., 2011). The well-established association between obesity and widespread musculoskeletal pain, even in non-weight-bearing sites, underscores the complex interplay between weight status and pain in FMS (Mork et al., 2010).

The high prevalence of overweight/obesity in women with FMS, the association between the level of physical conditioning and symptom severity, and the observed effects of controlled body weight and increased physical activity on FMS severity lead to the question of whether a causal relationship exists between these factors. While many studies are constrained by the cross-sectional nature of their designs, the cumulative evidence may contribute to a better understanding of these relationships. It remains uncertain whether decreases in physical conditioning and increases in body weight, either independently or in conjunction with other factors, act as triggers for the syndrome. Alternatively, these factors may be comorbid features or by-products, confounding variables of other etiological factors that play a more crucial role in triggering FMS. In this editorial, we will explore some potential perspectives to comprehend the intricate relationship between these variables.

Physical conditioning and fibromyalgia: a causal association?

We now understand that individuals with FMS exhibit more sedentary behavior, lower levels of physical activity, and poorer performance on functional capacity tests. Is this impaired physical status possibly linked to the onset of widespread pain syndrome? Some argue that inactivity and deconditioning are solely consequences of the burden of pain and disability. However, the relationship between them is evident even before the development of the syndrome, shedding light on the likely causal nature of these factors. It is well-established that sedentary behavior and a lack of adequate exercise can negatively impact health, affecting organ systems such as the cardiovascular, neuromusculoskeletal, and neuroendocrine systems, increasing the risk of developing chronic diseases (Anekwe et al., 2020).

Inadequate physical conditioning could thus represent a predisposing state for the initiation of pain processes, potentially evolving into a chronic state. Currently, there is no evidence that lower levels of physical conditioning alone could trigger the onset of widespread pain and hypersensitivity as observed in FMS, but they may set the stage for other environmental, genetic, and biological variables to come into play. Although longitudinal studies have not independently identified the risk of physically deconditioned individuals developing the syndrome, evidence suggests that, in addition to obesity, inactivity and lower levels of physical activity represent an increased risk for FMS over more than 10 years (Mork et al., 2010; Markkula et al., 2016).

On the other hand, as both are predictors, there may be a bidirectional relationship that is challenging to understand, as deconditioning can lead to overweight/obesity or may be a consequence of it. In this context, longitudinal studies help to elucidate the potential independence between them. For instance, Mork et al. (2010) demonstrated that obese women with the same level of activity as normal-weight women displayed a higher risk for FMS, highlighting the possibly independent role of obesity as a risk factor.

Obesity and FMS: a potential causal association

Increased BMI is prevalent in most women with FMS and represents a strong risk factor associated with symptom severity. The question arises: is obesity the main trigger for the onset of this syndrome? Is it a direct etiological cause, or is it a confounding factor for other variables that coexist with or cause obesity? The fact that some overweight women do not develop FMS while some normal-weight women do suggest that FMS likely has a multifactorial cause. However, obesity may still be an important variable to consider considering the systemic effects it brings about.

Obesity is characterized by systemic inflammation, a feature also observed in FMS. One possible explanation is that obesity alters the organic system, inducing a proinflammatory state that becomes chronic and renders the system prone to widespread pain, peripheral/central sensitization, neuropathic pain, and hyperalgesia (Mork et al., 2010; Patucchi et al., 2003). Supporting this explanation, an association between pro-inflammatory cytokines and BMI in FMS

is known (Ursini et al., 2011). A second shared feature between obesity and FMS is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. An increase in the norepinephrine/epinephrine and norepinephrine/cortisol secretion ratio is observed, correlating with a waist-hip ratio in FMS and obese women compared to healthy adults (Mork et al., 2010; Çakit et al., 2017).

A third shared characteristic is autonomic dysfunction, represented by the overactivation of the sympathetic input and reduced reactivity, primarily measured by heart rate variability (HRV). This system's impairment in response to stress and pain inhibition can contribute to the onset of clinical symptoms, such as sleep disturbance and fatigue (Mork et al., 2010). Therefore, it seems that obesity - whether directly or secondary to a biological or environmental cause - can disrupt the body's homeostatic state, making it more prone to what we now identify as FMS (Patucchi et al., 2003). Partial reversal of this process may be possible, as strategies targeting weight loss, such as physical exercise, diet, and bariatric surgery, have proven efficacious in reducing the severity of clinical symptoms, including pain (Schrepf et al., 2017).

As obesity may be a consequence of inadequate levels of physical activity, deconditioning becomes a relevant factor in the primary prevention of FMS. Increasing levels of physical activity and losing weight both have an effective impact on the clinical presentation of FMS. Physical conditioning emerges as a potential protective factor against inflammation, autonomic dysregulation, peripheral neuropathy, and dysregulation of the inhibitory pain system and pain networks. It likely helps maintain the system closer to a homeostatic state. Notably, some studies have observed a dose-response effect, indicating that women who engaged in physical activity four or more times per week had lower risk rates for FMS compared to inactive or less regular counterparts (Mork et al., 2010). Therefore, these strategies are crucial to break the cycle of weight gain and inactivity and mitigate their consequences in FMS, irrespective of the causal relationship.

Confounding as the basis for the relationship

The relationship between fibromyalgia syndrome (FMS), obesity, and physical activity is complex and multifactorial due to the presence of several potential confounders. These confounding factors are variables that have relationships with both the predictor variables (e.g., obesity, physical conditioning) and a determined outcome (e.g., FMS). They may offer alternative explanations for the supposed associations found between these variables. Potential confounders for the relationship between physical conditioning, obesity, and FMS encompass sociodemographic, clinical, and pathophysiological factors.

Demographic variables such as gender and socioeconomic status may play a role in accounting for obesity and inactivity/deconditioning, given that FMS is more prevalent in women compared to other chronic pain conditions. Additionally, obesity is prevalent in women with low socioeconomic status, often characterized by lower levels of education and social security. This lower socioeconomic status can lead to fewer opportunities and conditions for maintaining adequate physical activity levels (Anekwe et al., 2020; Cooper et al., 2021). Within the context of this demographic link, psychosocial distress may mediate the impact of low socioeconomic status, with implications for some proposed etiological causes of FMS, as mentioned earlier. This is particularly relevant for understanding the dysregulation of the endogenous inhibitory pain system and central pain processing networks.

Clinical variables such as sleep disturbance, stress levels, and mental health disorders may further serve as confounding factors in the relationship with obesity. Sleep disturbance is a common symptom in FMS, presenting as insomnia, altered sleep time, and reduced efficiency. Sleep deprivation or unrefreshing sleep can lead to psychological distress and chronic pain, such as chronic headaches or regional pain, potentially evolving into a chronic condition and contributing to the adoption of sedentary behavior and weight gain (Markkula et al., 2016; Keskindag and Karaaziz, 2017).

Similarly, stress levels and mental health disorders can be considered confounding factors, as they are associated with both weight gain and decreases in physical activity. The triggers for stress and psychological burden can be multifactorial, yet they often point to the same mechanisms responsible for chronic pain and psychological disorders like depression, anxiety, and eating disorders (Ursini et al., 2011).

Physical conditioning and obesity are intrinsically correlated, as we discussed, with obesity being a predictor of FMS diagnosis independent of physical fitness levels. However, the level of physical conditioning may likely play a role as an effect modifier, with lower levels of physical activity in obese individuals explaining the greater risk for FMS and disability. Conversely, physical conditioning itself can act as a confounding factor, as more severe levels of disability may negatively impact motivation and adherence to physical activity, resulting in inactivity, obesity, and the observed levels of exercise intolerance and fatigue in these patients (Pastor-Mira et al., 2021; Nijs et al., 2013).

Among the potential pathophysiological confounding factors, inflammation emerges as one of the most significant. Proinflammatory processes are shared by obesity and FMS, although the mechanisms behind this association still require consensus and further research. Therefore, when investigating overweight and obesity as predictors, what we may be measuring is the concurrent process of systemic inflammation—a likely etiological factor contributing to the onset of FMS (Bäckryd et al., 2017; Littlejohn and Guymer, 2018). This could explain why normal-weight individuals also develop the syndrome, albeit with lower probability, as the underlying cause would be the proinflammatory process. However, this is a hypothesis that needs further testing, especially since the triggers for this supposed inflammatory process are not yet understood (Ursini et al., 2011). It can be hypothesized that inflammation may serve as a mediator for several of the confounding clinical factors described above, such as sleep disturbance, stress, and mental disorders. As discussed, the evidence supports the benefits of weight loss and the effects of physical training on symptoms, including inflammation markers, emphasizing the relevance of this factor, against which exercise may exert a protective effect.

The cumulative evidence does not allow us to draw strict conclusions regarding the relationship between physical conditioning, obesity, and FMS. Most studies have a cross-sectional and retrospective design, introducing some important limitations. However, some longitudinal investigations have been conducted, providing relevant preliminary findings. Therefore, there are at least some possibilities to explore these variables and the potential causal relationship with the development and pathophysiology of FMS. Understanding the causal relationship and the possible contribution of confounding factors will be crucial for designing and interpreting clinical research, which is paramount for advancing the field. Regardless of the mechanisms and causal relationships, controlling body weight and exercising are positive and efficacious strategies to be included in the management of this condition. Further research is warranted to clarify the association with the pathophysiology of FMS.

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Conflicts of Interest

The authors declare no conflict of interest.

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