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Edgard de Melo Keene von Koenig Soares

PREVALÊNCIA DE HIPOGONADISMO DE INÍCIO TARDIO, DE SÍNDROME METABÓLICA E DE OBESIDADE EM BOMBEIROS MILITARES, EM ASSOCIAÇÃO COM A APTIDÃO CARDIORRESPIRATÓRIA E FATORES DE RISCO CARDIOVASCULAR: UM ESTUDO EXPLORATÓRIO

Orientador: Prof. Dr. Luiz Guilherme Grossi Porto

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Tese apresentada ao Programa de Pós-Graduação em Educação Física da Universidade de Brasília como requisito para obtenção do título de Doutor em Educação Física.

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FACULTY OF PHYSICAL EDUCATION
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RESUMO

Bombeiros são expostos a diversos fatores de risco à saúde e por isso há grande preocupação com a saúde destes profissionais, particularmente os aspectos cardiometabólicos. O hipogonadismo de início tardio (HIT), caracterizado por baixos níveis de testosterona e a presença sinais e sintomas como fadiga, falta de libido e redução do desempenho físico, pode estar associado a maior risco cardiometabólico e menor qualidade de vida (QV) nestes profissionais. Além disso, baixos níveis de testosterona em homens estão comumente associados com outras condições em que há o aumento de risco cardiovascular, como a síndrome metabólica (SM) e a obesidade (Ob). Contudo, o HIT é pouco investigado, e sua prevalência é desconhecida em bombeiros. Selecionamos aleatoriamente, em uma amostra enriquecida, 328 bombeiros militares que realizaram exame de sangue e responderam um questionário que incluía perguntas sobre atividade física, QV, sinais e sintomas de hipogonadismo e qualidade do sono. Foi utilizada a técnica de ponderação pela probabilidade inversa para estimar a prevalência de HIT, SM e Ob. Dados foram descritos utilizando mediana e quartis (dados não paramétricos) e diferenças foram consideradas significativas quando $p<0,05$. A força da associação entre a prevalência de HIT, SM, Ob, e aptidão cardiorrespiratória (ACR) foi analisada usando o teste de qui-quadrado e a razão de chance (OR) com o respectivo intervalo de confiança de 95%. Foi analisada a correlação (Spearman) entre os níveis de testosterona total (TT) e os quatro domínios da QV, idade, índice de massa corporal (IMC), ACR e escore de risco cardiovascular de Framingham (ERF). A prevalência estimada de HIT, SM e Ob foi de foi de 3,2%, 17,0% e 16,9% respectivamente. Houve significativa associação corrigida por idade entre HIT e SM (OR 21.3; 7.0-64.2) e Ob (OR 41.7; 9.2-189.9). Houve significativa correlação entre níveis de TT e idade (rs = -0,35; $p<0.01$), IMC (rs = -0,46; $p<0.01$), VO2max (rs = 0,45; $p<0.01$) e ERF (rs = -0,42;$p<0.01$). Quanto a QV, houve correlação significativa somente com o domínio físico (rs = 0,20; $p<0.01$). Não houve correlação significativa com a qualidade do sono (rs = -0,05; p=0.38). Identificou-se, de modo inédito, a prevalência de HIT em bombeiros, e fatores associados. Apesar da baixa prevalência de HIT, observou-se associação a significativos fatores de risco cardiovascular como a síndrome metabólica e obesidade que podem contribuir de forma deletéria para a saúde do bombeiro militar. As prevalências encontradas, e suas associações, são especialmente preocupantes nesta população, tendo em vista as rotineiras demandas físicas e emocionais inerentes à profissão, assim como seu elevado risco à saúde.

Palavras-chave: Baixa testosterona, aptidão física, saúde cardiovascular.

ABSTRACT

Firefighters are exposed to several health risk factors, and therefore there is great concern about the health of these professionals, especially the cardiometabolic aspects. Late-onset hypogonadism (HIT), characterized by low testosterone levels and the presence of signs and symptoms such as fatigue, lack of libido, and reduced physical performance, may be associated with higher cardiometabolic risk and lower quality of life (QoL) in these professionals. . In addition, low testosterone levels in men are commonly associated with other conditions where there is an increased cardiovascular risk, such as metabolic syndrome (MS) and obesity (Ob). However, HIT needs to be better investigated, and its prevalence is unknown in firefighters. In an enriched sample, we randomly selected 328 military firefighters who completed bloodwork and answered a questionnaire that included questions about physical activity, QOL, signs and symptoms of hypogonadism, and sleep quality. The inverse probability weighting technique was used to estimate the prevalence of HIT, MS, and Ob. Data were described using median and quartiles (non-parametric data), and differences were considered significant when $p<0.05$. The strength of the association between the prevalence of HIT, MS, Ob, and cardiorespiratory fitness (CRF) was analyzed using the chi-square test and the odds ratio (OR) with the respective 95% confidence interval. The correlation (Spearman) between total testosterone levels (TT) and the four domains of QOL, age, body mass index (BMI), CRF, and Framingham cardiovascular risk score (FRS) was analyzed. The estimated prevalence of HIT, MS, and Ob was 3.2%, 17.0%, and 16.9%, respectively. There was a significant age-corrected association between HIT and MS (OR 21.3; 7.0-64.2) and Ob (OR 41.7; 9.2-189.9). There was a significant correlation between TT levels and age ($r_s = -0.35$; $p<0.01$), BMI ($r_s = -0.46$; $p<0.01$), VO_2max ($r_s = 0.45$; $p<0.01$), and ERF ($r_s = -0.42$; $p<0.01$). As for QOL, there was a significant correlation only with the physical domain ($r_s = 0.20$; $p<0.01$). There was no significant correlation with sleep quality ($r_s = -0.05$; $p=0.38$). An original finding of this study was identifying the prevalence of HIT in firefighters and its associated factors. Despite the low prevalence of HIT, there was an association with significant cardiovascular risk factors such as metabolic syndrome and obesity that can be deleterious to the health of military firefighters. The prevalences found and their associations are especially worrying in this population, given the routine physical and emotional demands inherent to the profession and its high health risk.

Keywords: Low testosterone, physical fitness, cardiovascular health

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1. PREAMBLE

Firefighters perform essential work for society and, in Brazil, are one of the most respected and admired public servants. This praise is not unearned. They are dedicated public servants, and their profession casts a heavy toll on their health and well-being. Fortunately, different research areas have been dedicating their efforts to better understand health risks related to firefighting. A search on Medline looking for “firefighters,” OR “fire service” OR “firemen” combined with “health” in title/abstract resulted in 493 publications from 1954 to today. Among those 493 papers, approximately 90% (443) were published from the year 2000. So, scientific research on firefighters´ health and its association with job-related activity may still be considered as a new research area. Despite its relatively young age, this research field has rapidly evolved, arousing interest from different areas, such as occupational health, exercise sciences, medicine, engineering, physics, rehabilitation, among others. Undoubtedly, all involved scientists would love to be able to completely mitigate the risk of firefighters´ professions. Unfortunately, it is impossible to “turn the heat off”. Fires will always be dangerous, and a call for rescue can not wait a good night of sleep. Brasilia, as local example, has a severe season of wildland fire every year which is very taxing to our firefighters. If we can not “turn the heat off,” what can we do to ameliorate this? Can we “blow a breeze” to help “cool down”?

Firefighter-related research has brought to light important aspects to improve the health and quality of life of these professionals. Research results have helped improve personal protective equipment, increase rest days between 24-hour shifts, and increase recovery periods between firefighting bouts. Besides structural changes, research has also brought to light similar findings in the general public. We highlight the importance of cardiorespiratory fitness (CRF) to health, well-being, and work performance. High CRF has been constantly associated with lower prevalence rates of cardiovascular risk factors. Muscular fitness has also been associated with lower mortality rates. So where does a Ph.D. thesis developed in the Graduate Program in Physical Education (PPGEF – Portuguese acronym) of the University of Brasilia (UnB) fit into this?

The University of Brasilia - UnB has been collaborating with the Fire Service for a long time. This collaborative work resulted in significant gains for both institutions and has brought forth an entire line of research currently linked to the GEAFS (Research Group on Physiology and Epidemiology of Exercise and Physical Activity) housed at the Faculty of Physical Education and the PPGEF. Led by Prof. Porto, this thesis advisor and one of the founders of the GEAFS study group, this research line has prospered over the last eleven years of scientific publications and important international collaboration. Investigating the relationship between physical activity and health-related physical fitness (HRPF) with varied health conditions and cardiometabolic risk factors are defining characteristics of our work. Regarding the Fire Service, we keep moving forward, trying to help “cool down” those constantly under the toll of the “heat.”

Work of this thesis, innovative research, we investigate the prevalence of conditions that increase the cardiovascular and metabolic risk of firefighters while possibly decreasing their quality of life. We also investigate how HRPF (here, CRF and body composition) is associated with these conditions and different risk factors. Despite not encompassing the work presented here, we are also taking another step forward, investigating interventions to increase HRPF and improve the conditions of firefighters with the mentioned conditions. We end this preamble by mentioning that while to some, our work goes beyond what would classically be understood as a Physical Education theme, we believe, for the reasons above, that an analytical prevalence study on conditions that harm health and quality of life of firefighters while associating with HRPF is very well housed here in the PPGEF. Our hope is that may be a “cool breeze” in the middle of the firefighters’ heat.

2. INTRODUCTION

Firefighters (FF) work day and night for the well-being of their communities. Despite their dedication, the nature of their profession implies great hazards, with elevated physiological and psychological strain (SMITH et al., 2016). For example, a live-fire training drill elicited a peak heart rate (HR) response equivalent to 100% of the aged predicted maximal HR, in some cases, sustained for several minutes. A similar result was observed during a specific training course using self-contained breathing apparatus (WILKINSON et al., 2020). A study that evaluated the intensity of the physical activity performed by firefighters during wildland fire suppression showed that they could achieve more than 110 minutes on vigorous intensity (>76% and < 94% of age-predicted max. HR) and more than 30 minutes on very vigorous intensity (>=94% of age-predicted max. HR) (MARTIN et al., 2020)

The tasks themselves are already physically taxing, but firefighters have to execute them wearing personal protective equipment (PPE) weighing up to 20 kg or more (NOGUEIRA et al., 2021; PORTO et al., 2020). A study investigating energy costs in typical firefighting duties observed 10-13 METs during such activities (WILLIAMS-BELL et al., 2010). Due to physical exertion, a heat strain is associated with physical activity (PA), augmented by the PPE, and, when present, fire (HORN et al., 2013; WILKINSON et al., 2020). It is not surprising that fire suppression is one of the most dangerous activities that FFs perform, having 136 times higher odds of death from coronary heart disease compared to nonemergency duties (KALES et al., 2007). Unfortunately, sudden cardiac death (SCD) has been the leading cause of line-of-duty death in the United States (US) for more than 30 years when not considering COVID-19-related deaths (FAHY; PETRILLO, 2022). While law enforcement professionals have up to 10% line of duty deaths due to SCD, which is already a considerable percentage, almost 50% of on-duty fatalities are due to SCD, highlighting the risk and physiological strain of their work (VARVARIGOU et al., 2014). Also, there is an estimated 17 non-fatal cardiovascular event for every SCD in the line of duty (SMITH; BARR; KALES, 2013). Numbers like this have motivated multiple studies to understand better firefighting physiological strain and the investigation of risk factors and underlying diseases that could “tip the scale” to trigger an SCD event (KALES; SMITH, 2017; SMITH et al., 2016; SMITH; BARR; KALES, 2013; SOTERIADES et al., 2011). More recently, a case-control study based on national US autopsy data showed that more than 50% of cases of sudden cardiac death had evidence of a prior myocardial infarction compared with 6.6% of the noncardiac trauma control group (SMITH et al., 2018).

There currently is no available similar data in Brazil, but there seem to be considerably fewer line-of-duty deaths. However, this does not mean there is no health burden accumulated over the years of firefighting. Research data from FF centers point towards a lower life expectancy of almost six years compared to the general male population (SANTOS, 2009). These data connect us to a larger scope, in which, despite the unequal number of fatalities, research in cardiovascular risk and protective factors, Brazilian military FFs may contribute to the broader knowledge of FF's health. Throughout the years, formidable advances have been made in this field of expertise. The autopsy studies were a turning point for a greater focus on subclinical conditions and risk factors. A thorough investigation of all available autopsy records between 1999-2014 in US FF showed that cardiomegaly, severe coronary stenosis, and prior infarction were significantly associated with deaths in the line of duty (SMITH et al., 2018). In another step forward, 80% of duty-related cardiac deaths had evidence of coronary heart disease and cardiomegaly. Also, the odds of cardiac-related death during or after fire suppression were 112 times greater than fire station duties (SMITH et al., 2019). Thus, scientific investigation increased its focus on the "cardiac" part, like investigating subclinical cardiac dysfunction in FFs (SMITH et al., 2022).

Accordingly, we turned our eyes to other risk factors that could contribute to pathologic cardiac alterations. Recently, the possibility of serum total testosterone (TT) as an indicator of cardiovascular (CV) and metabolic health have been investigated. TT levels have been linked to endothelial dysfunction (AKISHITA et al., 2007) and cardiovascular events in Asian men, even when adjusted for multiple confounders (AKISHITA et al., 2010). The culmination of this are the recent meta-analysis indicating a low TT as an independent predictor of CV mortality and morbidity (CORONA et al., 2011b, 2018). Interestingly, low TT is strongly associated with obesity, presenting prevalence rates as high as 80%, depending on the severity of obesity and the cut-off point (ZAROTSKY et al., 2014). Also, low TT and metabolic syndrome (MS) are significantly associated with each other in a bidirectional way, although a causal link has not been established (BERG; MINER, 2020; CORONA et al., 2011a; DIMOPOULOU et al., 2018). We have investigated the relationship between low serum TT in US FFs and have obtained important findings on this matter. First, we observed a high prevalence of low TT (10.6%) in a sample of Florida career FFs performing a routine medical examination. This was the first study to report prevalence data of low testosterone levels in the US fire service. In this study, we also observed an association between serum TT left ventricular wall thickness (LVWT), suggesting a possible relationship between borderline TT levels and lower LVWT. This “mildly decreased TT levels and lower LVWT might represent a preclinical condition and a window of opportunity for cardiovascular preventive interventions in firefighters.”(LOFRANO-PORTO et al., 2020). The novel finding of this study led the authors to propose an hypothetical model for the complex interaction between TT, traditional cardiovascular risk factors and the cardiac structure (Figure 1 – not published). This model will certainly evolve to more complete scheme but illustrate the importance of investigating the role of TT on cardiovascular system.

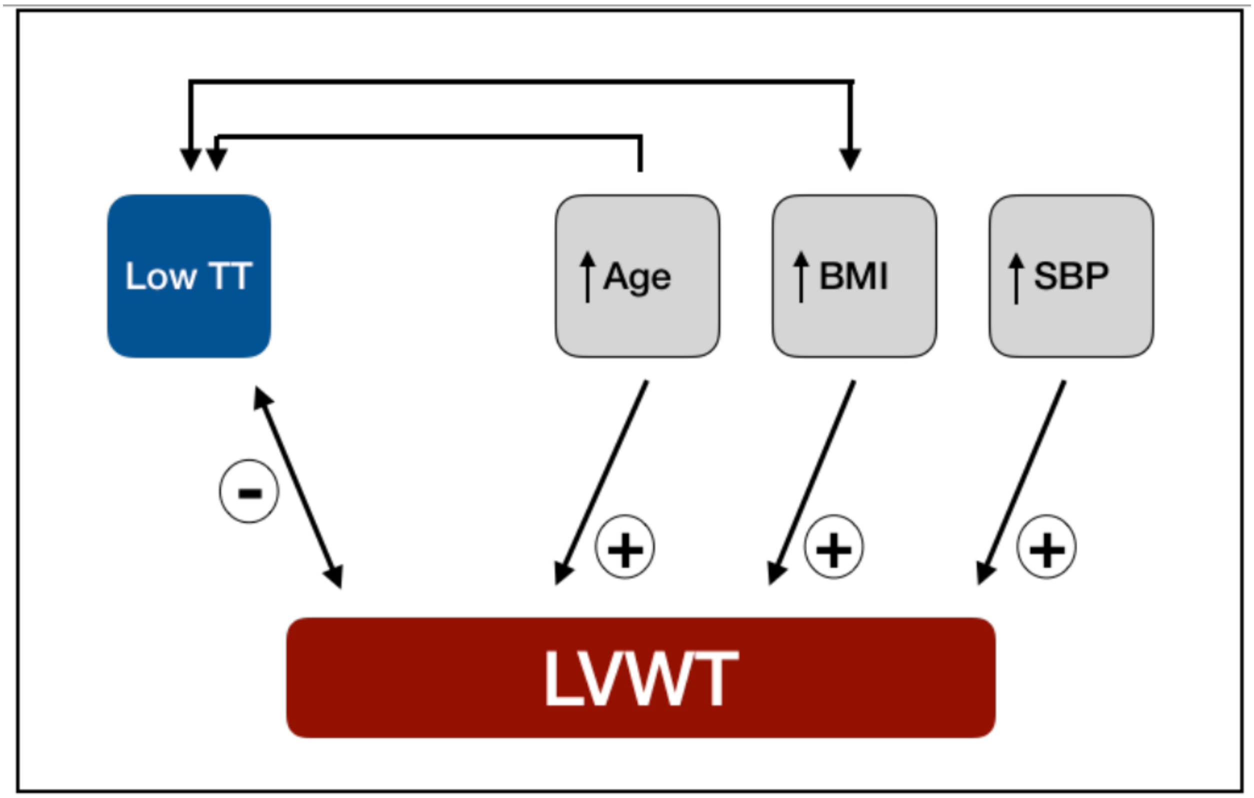

Figure 1: Hypothetical model for the complex interaction between TT, traditional cardiovascular risk factors, and the cardiac structure (from Lofrano-Porto A, Soares E, Porto LGG, and Smith D – unpublished)

In a real-world study of 298 US male firefighters evaluating low testosterone levels and cardiometabolic risks factors, we also observed a significant association between low

TT and a worse cardiometabolic profile, including having fatty liver, high HbA1c and high triglycerides even when adjusting for age and body mass index (BMI) (RANADIVE et al., 2021).

It is essential to highlight that investigating the relationship between testosterone levels, especially endogenous testosterone levels, is a current research theme of interest. A simple search on the Medline-Pubmed database with the terms "testosterone" AND "cardiovascular risk" resulted in 824 findings. Among them, 769 (93%) were published from the year 2000, and 472 (57%) in the last ten years. When substituting the word "testosterone" with "endogenous testosterone," the respective numbers are 29, 28 (97%), and 62%. Using yet a third different term, the numbers that resulted in a search with "serum testosterone" instead of only "testosterone" are 103, 95 (92,2%), and 61 (59%). There is no doubt that other search terms would result in different findings, but those examples show the theme's novelty and how timely our study is. In summary, in all search terms, we found that almost all published work occurred from 2000 (>90% of the cases), and around 59% were published in the last decade.

Taking a step forward, it is necessary to investigate not only low TT levels but hypogonadism, specifically late-onset hypogonadism (LOH). Briefly, this condition is characterized by low levels of testosterone and a myriad of signs and symptoms, some customarily referred to as specific (mainly: reduced sexual libido, erectile dysfunction) and nonspecific (sleep disturbance, decreased energy, increased body fat, reduced muscle bulk strength) (BHASIN et al., 2018; TAJAR et al., 2012; TRAVISON et al., 2017). Importantly, none of those sign and symptoms would be desired in the Fire Service, considering the high physical and psychological demands of the profession that does not fit with low levels of human performance.(AL-ZAITI et al., 2015; HORN et al., 2013; NATIONAL FIRE PROTECTION ASSOCIATION, 2007; SOTERIADES et al., 2011) Per Endocrine Society guidelines (BHASIN et al., 2018), characterization of LOH requires assessment of signs and symptoms and confirmed low testosterone values by performing two separate measures. It is crucial to determine the prevalence of LOH since this group might require specific treatment and not only lifestyle modifications(BHASIN et al., 2018). Serum TT is highly associated with BMI, and in individuals with obesity, low serum TT can be normalized by weight loss (PELLITERO et al., 2012). Besides a greater CV and cardiometabolic risk, individuals with LOH might also have decreased quality of life(TAJAR et al., 2012); this might be worse in the Fire Service since firefighters are already exposed to significant physical and psychological stressors due to the nature of the work, e.g., sleep disorders, which also are associated with LOH, might also be “entangled” with further reductions in quality of life (CAREY et al., 2011; MARCONATO; MONTEIRO, 2015). Currently, the prevalence of LOH in the Fire Service is unknown but probably lower than estimated by one measurement of testosterone due to requiring confirmed low testosterone and signs and symptoms (ZAROTSKY et al., 2014). Understanding the prevalence rate helps us understand the “size” of the problem. Since LOH is associated with metabolic syndrome – which significantly increases cardiovascular mortality and morbidity risk – and obesity, this further opens up an opportunity to investigate these associated conditions and analyze their relationship with cardiovascular and metabolic risk.

Thereafter, by combining: 1) firefighters' physical and psychological job-related stressors; 2 – the symptoms of LOH and its probable undesired consequences on firefighters' health, safety, and job performance; 3 – the potential association and inter-relationships between traditional cardiometabolic risk factors, LOH, low TT, metabolic syndrome and obesity; 4 – the fact that reduced serum TT values have been associated with a worst cardiometabolic profile and with possible impact on the cardiac structure; 5 – the fact that physical training and lifestyle modification strategies have been shown to prevent or mitigate various traditional and novel cardiovascular risk factors, we aimed to investigate the prevalence of late on-set hypogonadism, metabolic syndrome, and obesity, and associated factors in male career military firefighters.

3. GOALS

3.1. PRIMARY AIM

To determine the prevalence of late on-set hypogonadism, metabolic syndrome, and obesity and associated factors in male career military firefighters.

3.2. SECONDARY AIMS

To compare the different forms of evaluating hypogonadism and low testosterone and its impact on their estimated prevalence.

To assess the association between hypogonadism, metabolic syndrome, obesity, and cardiorespiratory fitness among male career military firefighters.

To compare characteristics, particularly cardiovascular risk and cardiorespiratory fitness, of male career military firefighters with hypogonadism to those without hypogonadism.

To explore the relationship between serum total testosterone levels and cardiovascular risk factors.

To compare the characteristics of FF within specific ranges of serum total testosterone levels.

4. METHODS

4.1. STUDY DESIGN

We utilized a cross-sectional design to investigate the prevalence of male late-onset hypogonadism (LOH), metabolic syndrome (MS), and obesity in Brasília's firefighters (FFs). We randomly selected 360 FFs using an "enriched" randomization strategy based on age, obesity, and cardiorespiratory fitness (CRF) to increase the selection of participants at-risk for LOH (Figure 2). Thus, our sample was composed in a two-step process. First, we randomly selected FFs from the eligible population to compose 25% of the sample. Then, we randomly selected FFs considered as having a higher risk for hypogonadism to compose 55% of the sample. Lastly, we selected FFs considered as having a lower risk for hypogonadism to compose the remaining 20% of the sample.

High-risk and low-risk FFs were classified using variables traditionally associated with testosterone levels, BMI, and age (BHASIN et al., 2018; DANDONA; ROSENBERG, 2010; PELLITERO et al., 2012). Although not as robustly as prior variables, CRF has been otherwise associated with testosterone levels (DEFINA et al., 2018; GAGNON et al., 2018), and is associated with obesity and metabolic syndrome, another outcome of interest in this research (BAUR; CHRISTOPHI; KALES, 2012; NOGUEIRA et al., 2016). High-risk FFs were those with obesity (BMI ≥ 30.0) and at least one other risk factor, age (≥ 40 years), or low CRF. FFs considered to have a low risk for hypogonadism were those who did not have obesity (BMI<30.0), were younger (< 40 years), and had high CRF.

To classify CRF, we utilized the results of the aerobic tests performed in the CBMDF, the Cooper test (12-minute run), a 12-minute swimming test, and a 15-minute walk/run test for those with an age of ≥ 50 years. FFs can choose between the swimming and the running test when younger than 50 years. From 50 years old onward, FFs must perform the 15-minute walk/run test. Of all tests, the most frequent was the running test (88.5%), followed by the swimming one (7.8%). The 15-minute walk/run is age-restricted and thus encompasses a very small part of the sample (3.7%). Results were classified according to the Cooper test's criteria or based on calculated tertiles for the swimming and walk/run tests. For the latter tests, high CRF was defined as having results equivalent to the highest tertile of the sample, while low CRF was considered to be in the lowest tertile. Cooper's classification has six "levels": very poor," "poor," "fair," "good," "excellent," and "superior." FFs in the "poor" or "very poor" categories were classified as having low CRF. For high CRF, FFs had to be classified as having a "good," "excellent," or "superior" result. The sampling process, calculated sample size, and CRF criteria are summarized in figure 2.

To calculate our sample size, we considered the total population of male FFs who performed the annual physical exam in 2019 (n=4027). The prevalence of secondary hypogonadism may vary from 2.1 up to 24.2% depending on age and criteria used to classify it (ZAROTSKY et al., 2014). Thus, considering the other outcomes of interest (obesity and metabolic syndrome), we inputted the prevalence as 50% for our calculation to obtain the largest sample size possible, with a 5% margin of error and a 95% confidence level. We estimated a sample size of 351 FFs. To account for study drop-outs and exclusions, we increased the estimated sample size to 360 FFs.

4.1.1. Study design updates due to the COVID pandemic

Due to the tragic COVID-19 pandemic and the sanitary situation in Brazil, our study had to be interrupted. Significant changes were necessary for the data collection process to adapt to our new reality. Until it was safe and changes were in effect in all institutions involved in this research, we interrupted the study for almost a year and a half. Despite changes to the data collection process, no changes were made to the study design. Volunteers were still being drawn from the 2019 database. However, due to the time difference, we were worried that some FFs could have changed their fitness levels (CRF or BMI); thus, their risk category would need to be updated. Therefore, we sought new physical fitness data as soon as they were available. Unfortunately, no physical fitness tests were performed in 2020 because of the COVID-19 pandemic. A new database was only available to us in January 2022. With this new data, we updated the risk categories of the FFs and performed the sampling process again. We followed the same steps, drawing FFs to complete the expected sample size.

Lastly, for the data analysis, we updated their risk category again to account for all the time differences and better reflect the volunteer's state when performing the blood work. This time we considered the age and BMI when the questionnaire was answered, but the CRF value was the closest to their study participation. 3.6% (11 FFs) of the 2021/2022 volunteers did not have 2021 fitness test values, so we used 2019's results.

We believe this methodological change strengthens our data since we used the most recent data available to classify our participants. Consequently, if necessary, some FFs drawn for the high-risk group may be removed from this category—for example, a FF who was not obese anymore during data collection. If a volunteer presented data that differed from the group where he was initially drawn, he was counted as coming from the overall draw since all draws were randomized.

Population

4027 male FFs that did the physical fitness assessment in 2019

1st selection step

Total Sample

Simple random selection of 25% of the sample **(90)**

2nd selection step

(excluding those already selected in the 1st step)

Low-risk group
20% of the sample
(72)

BMI < 30 kg/m^2
AND
Age < 40 years
AND
High CRF

High-risk group
55% of the sample
(198)

Obesity (BMI >= 30 kg/m^2)
AND
Age >= 40 years
OR
Low CRF

CRF will be assessed by:

- 12-min Cooper test (88.5% of the population)
- 12-min swimming test (7.8% of the population. This is a definition made by the FF's own decision as a surrogate for the running test)
- 15-min walk test – mandatory for >= 50 years (3.7% of the population)

Low CRF will be defined as:

- Two lowest age/gender categories of the Cooper test
- Lowest tertile on the swimming test
- Lowest tertile on the 15-min walk test

High CRF will be defined as:

- Three highest age/gender categories of the Cooper test
- Highest tertile on the swimming test
- Highest tertile on the 15-min walk test

Obs.: Tertiles were used for the swimming and walk tests because there are no standard categories for those two tests.

Figure 2. Overview of the sampling process and cardiorespiratory fitness (CRF) criteria.

4.2 RESEARCH ETHICS STATEMENT

The study was planned and performed following the Declaration of Helsinki and relevant guidelines and regulations. The study protocol was approved by the University of Brasilia Health Science Human Research Ethics (CAAE: 80792017.8.0000.0030). Participation was voluntary, and all participants gave written informed consent. The CBMDF also approved our research protocol and provided support and necessary authorization for data collection.

4.3 STUDY SETTINGS

This study recruited male FFs from Brasília, Brazil, in two time periods: January/2020 until March/2020 and July/2021 until August/2022. The first part of the data collection was done in person, with the research team visiting different FF units all over the Federal District of Brazil. In the second moment, the research team connected potential participants via phone messages using the Whatsapp and Whatsapp Web applications. Again, we highlight that this change was necessary due to sanitary conditions, i.e., the COVID-19 pandemic, and it was the best way to continue the data collection while minimizing risks for everyone involved in the research (volunteers, research members, laboratory facilities, etc.).

4.4 PARTICIPANTS

Male military firefighters who performed a physical fitness assessment in 2019 or 2021 were invited to participate in this study. Per the study design, we randomly selected individuals to be invited to participate. To be eligible, FFs needed to be without any restrictions to serve and perform the physical fitness testing. Also, FFs should be active in the CBMDF, which meant that FFs who retired or were assigned to work under another part of the public service not directly related to duty performed by the CBMDF (e.g., Justice Ministry) would not be included. The final sample of this study was composed of 328 male firefighters aged between 24-55 years with a body mass index varying between 20.6 to 40.9 kg/m^2. This final sample size, using the prevalence estimate of 50% and a confidence interval of 95%, resulted in a margin error of 5.19% instead of 5%. However, using a prevalence estimate of 25%, based on previous estimates of the most prevalent outcome of interest – obesity (NOGUEIRA et al., 2016; SEGEDI et al., 2020), our final sample size resulted in a margin error of 4.49%, showing that our sample size overcame the minimum sample size necessary to adequately estimate the population prevalence with a confidence interval of 95% and a margin error of 5%. Also, we had surpassed the proposed minimum number of low-risk and neutral-risk FFs but could not reach out to more high-risk FFs.

4.4.1 Exclusion criteria

The following exclusion criteria were adopted:

- Use of testosterone-increasing substances within the last six months;
- Did not perform bloodwork;
- Retirement;
- Working under another part of the public service outside of the Fire Service scope.

Regarding the 2020 part of the study, we had 33 FFs who agreed to participate. Of those, only 20 completed their participation by performing the bloodwork. One FF retired before completing bloodwork and later declined to continue participating. One FF did not perform the blood work due to lack of time. The remaining 11 FFs did not get their bloodwork done because of Brazil's COVID-19 outbreak and quarantine. When data collection returned in 2021, all 11 were reached again, but seven declined to participate for various reasons, primarily due to lack of interest or time.

The 2021/2022 part of the study used text messages and phone calls in an "in-distance" manner. This approach made asking "sensitive" questions harder, like anabolic steroid use. Because of this, the number of exclusions was increased compared to the previous research period, e.g., in the 2020 part, no FF under steroid use answered the questionnaire because they were excluded before this. However, in 2021/2022, we were only able to exclude them after they completed the questionnaire because, in most cases, we were not able to ask them clearly. A total of 326 FFs completed our questionnaire, with three FFs answering twice (329 completed questionnaires) due to not performing bloodwork in the designated timeframe while undergoing significant changes in habits after the first time they responded. A total of 18 FFs were excluded, five due to recent testosterone use, one due to retirement, one due to be currently working outside the

CBMDF, and the last 11 due to not performing the blood work. Not completing the blood work was due to lack of time or interest. In summary, our sample comprised 20 volunteers from the 2020 part of the study and 308 from the 2021/2022 one.

4.5 DATA COLLECTION

Data collection happened in two different manners, in person and via messaging. In both parts, we would send the registration number of the selected FFs to the CBMDF, which in turn sent back the necessary information to reach the FFs. During the in-person phase, this meant mainly full name and unit. During the second phase, we would also receive cellphone numbers. In both stages, to confirm hypogonadism or borderline testosterone values, the second measurement of total testosterone was requested when a FF presented a value of <400 ng/dL according to the Endocrine Society recommendation (BHASIN et al., 2018).

4.5.1. In-person procedures

In the first part of our study, all the data collection happened in person. After we received authorization from the CBMDF, we followed all institutional recommendations. First, we scheduled a visit with the commanding officer of the unit. After explaining the research to the commanding officer, we requested additional information to reach the selected FFs in that unit – full names and work schedules. The research team would visit the department to invite the firefighter to participate, perform the data collection, deliver a new request for bloodwork in case FFs lost the due date, give feedback on the bloodwork, provide the request for a second testosterone measurement (when necessary), and deliver second feedback when a second testosterone measurement was performed. Data collection happened in the most private setting we could get in a unit so that the participant felt comfortable talking to us and answering the questionnaire. We collected data on FFs from 12 departments from January to March 2020.

4.5.2. Messaging procedures

In this second part of our study, we adapted all the data collection process to a “distance” format using phone app messages (Whatsapp). After the CBMDF issued a new authorization, we started data collection following a similar pattern to the in-person procedures. We tried to reach the commanding officer of some units via phone. We tried contacting them first because we already had some commanders' phones. Most had already changed departments and often shared the new commander's contact. When we reached the commanding officer, we explained the research and that the CBMDF had already authorized our procedures; the commander or indicated personnel would share the name and phone numbers of the selected FFs.

Later, in October 2021, the CBMDF gave us new authorization to reach the selected FFs directly. We would send a list containing the registration number of the chosen firefighters to the CBMDF, who would share the names, phone numbers, and workplaces of the FFs. This new dynamic exponentially increased our capacity to get in touch with FFs.

We standardized that we would send three messages split by at least three days if we did not receive any reply from selected FFs. In our message, we explained that the CBMDF authorized our research, and we invited the FF to talk via phone call about the study. After acceptance, we will send the questionnaire link. We would also monitor when FFs answered the questionnaire, so we would only send the blood work request after completion. After FFs completed the questionnaire, we e-mailed a voucher for the blood work. We would then monitor them by sending reminders so they would retain the due date (3 weeks initially). After the results were available, we would get in touch to schedule feedback for their results and invite them for a second testosterone measurement when necessary. In case of values that differed from the Laboratory's reference criteria, we would also send a medical referral by e-mail.

4.6. MEASUREMENTS AND PROCEDURES:

In the first part of the study, after agreeing to participate and signing informed consent, the research team started with an anamnesis to obtain information about job activity, type of shift work, injury and health-related leave, income, regular exercise, and use of medication. Most importantly, this moment aimed to bond the participant so he could feel comfortable talking about previous testosterone measurements and the possible use of testosterone stimulants or hormones. As this was a critical exclusion criterion, we strived to make participants the most comfortable possible by ensuring that their data was confidential. No one would be aware of their answers about the previous use of testosterone-enhancing substances if it were the case. We also asked about any potential health issues they needed to disclose. Afterward, we measured blood pressure (BP) following standard procedures – sitting with legs uncrossed, 3-5 minutes rest, empty bladder, always left arm. A second measurement was performed in case of a systolic BP ≥130 mmHg or a diastolic BP ≥85 mmHg (BARROSO et al., 2021) and anthropometric data using standard procedures (height, weight, and waist circumference). Waist circumference was measured midway between the inferior margin of the ribs and the superior border of the iliac crest to account for metabolic syndrome components (ALBERTI et al., 2009). Subsequently, the volunteer sat in a private space to answer all the questionnaires.

In the second part, all of this happened online. The anamnesis was adapted to the online questionnaire, primarily to open-ended questions. Height and weight were self-reported since they are generally accurate measures (HSIAO et al., 2014; POSTON et al., 2014), but we no longer included waist circumference. The blood pressure measurement was also self-reported, with volunteers being instructed to prefer a digital sphygmomanometer or get help from a colleague to measure it during work while avoiding just recalling it from the last measurement.

4.6.1. Descriptive data

Through the questionnaire, we obtained descriptive such as age, weight, height, income, medication use, rank, type of work in the Fire Service, and years of service.

4.6.2. Physical activity level

We used the short version of the International Physical Activity Questionnaire (IPAQ) to assess regular physical activity (PA). IPAQ has been translated and validated in Portuguese for over 20 years (MATSUDO et al., 2001), having been successfully used to estimate PA levels in Brazil in various studies (HALLAL et al., 2007, 2010). The IPAQ short (ANNEX I) comprises six questions regarding weekly minutes and frequency of walking, moderate and vigorous PA. Questionnaires answers are about global PA, without separating leisure, work, or transportation.

To classify a volunteer as physically active, we followed the most recent World Health Organization recommendation (BULL et al., 2020). Thus, to be considered active, FFs needed to accumulate ≥ 150 minutes of moderate PA or ≥75 minutes of vigorous PA or an equivalent combination. Regarding the term “equivalent,” we understood that when combining moderate and vigorous PA, the minutes should be doubled for vigorous PA (150 vs. 75-minute recommendation). Defining this equivalence is important since doubling vigorous PA minutes did not significantly increase physically active prevalence in three representative Brazillian cohorts in which we previously tested this approach (SOARES et al., 2019) while respecting the energy expenditure concept that distinguishes exercise intensities overviewed in IPAQ’s scoring manual (IPAQ, 2005).

4.6.3. Maximal oxygen consumption estimation (VO_2max)

We used FFs' physical fitness test data to estimate VO_2max in FFs who performed the Cooper 12-minute run test. VO_2max was calculated as the total distance minus 504.9 divided by 44.73. Since some FFs performed the swimming test or the 15-minute walk/run test, we also estimated VO_2max using the self-reported physical activity (SRPA) questionnaire (ANNEX II). Briefly, FFs should choose between 8 items that describe distinct patterns of PA and exercise. VO_2max is estimated based on the selected answer, age, BMI, and sex. This questionnaire has been validated for the general adult population and used among FFs (JACKSON et al., 1990; POSTON et al., 2011). In Brazil, our research group translated the scale to Portuguese and observed a good agreement between SRPA-based VO_2max and the Cooper-based VO_2max in a sample of 702 male FFs (SEGEDI et al., 2020). Applying the SRPA questionnaire was necessary to have an estimated VO_2max for all FFs since some FFs performed swimming or run/walk tests that do not estimate VO_2max. So, estimated VO_2max based on Cooper, swimming, or 15-minute walk/run test were only used to classify FFs into risk groups before randomization. However, for all analyses, SRPA-based VO_2max was used since it is an accurate estimation and because this estimation was done based on data collected in the same period of volunteers´ participation (questionnaires and bloodwork data). We could not use Cooper-based VO_2max for the analyses because the length between the Cooper test performance and volunteer participation was too long, surpassing six months in many cases.

4.6.4. Sleep quality

We included the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality (ANNEX IV). The PSQI appraises sleep perception and dysfunction over 30 days using a questionnaire composed of 19 questions. The PSQI evaluates seven independent sleep components that reflect “sleep quality.” The calculated sleep index score can be used to classify individuals as having “good sleep quality” (PSQI ≤5) or “bad sleep quality” (PSQI >5).

4.6.5. Quality of life

To measure the quality of life (QoL), we used the Abbreviated World Health Organization Quality of Life questionnaire (WHOQOL–bref – ANNEX V). This questionnaire was designed to allow for a cross-cultural instrument to assess QoL. It has been translated and validated in Brazilian Portuguese (FLECK et al., 2000). WHOQOL-bref comprises 26 questions with four QoL domains: physical, psychological, social, and environmental (FLECK et al., 2000). Two questions are general QoL questions. Each domain is composed of the following items:

- **Physical domain:** 1- Pain and discomfort; 2- Energy and fatigue; 3- Sleep and rest; 9- Mobility; 10- Activities of everyday life; 11- Dependence on drugs or treatments; 12- Work capacity.
- **Psychological domain:** 4- Positive feelings; 5- Thinking, learning, memory, and concentration; 6- Self-esteem; 7- Body image and appearance; 8- Negative emotions; 24- Spirituality, religion, personal beliefs; 26- How often do you have negative thoughts.
- **Social domain:** 13- Personal Relationships; 14- Social support; 15- Sexual activity.
- **Environmental domain:** 16- Physical security and protection; 17- Home environment; 18- Financial resources; 19- Health and social care; 20- Opportunity to acquire new information and skills; 21- Participation and leisure opportunities; 22- Physical environment (pollution/noise/traffic); 23- Transport.

A QoL score can be calculated, ranging from 0-100 points. There are no official cut-points or normative criteria for the WHOQOL-bref results. Thus, scores were analyzed as the absolute value in the 0-100 scale, without units.

4.6.6. The Androgen Deficiency of the Aging Male (ADAM) questionnaire

The ADAM questionnaire has ten questions (ANNEX III). If the volunteer answers yes to questions 1 or 7, he has a positive criterion for late-onset hypogonadism (LOH), as well as if he answers yes to three or more questions (CLAPAUCH et al., 2008; MORLEY et al., 2000). Hereafter, this will be referred to as having a positive ADAM questionnaire (ADAM+). Those who answered ADAM and did not meet such criteria will be referred to as having a negative ADAM (ADAM-).

To the best of our knowledge, no version has gone through the process of cultural adaptation and validation into Brazilian Portuguese. However, it is used in clinical routine, for example, at Hospital das Clínicas in Porto Alegre (BLAYA, 2015; CABRAL et al., 2014) and in master's dissertations (BUZIN, 2010; TAHA NETO, 2016), it is also used in research as a form of quantitative/qualitative assessment of symptoms associated with LOH (SOARES et al., 2018). Clapauch et al. (2008) tried to relate the results of the questionnaire with biochemical tests in hypogonadal and non-hypogonadal patients as well as with osteoporosis and without osteoporosis and observed that the question that best related to bioavailable testosterone was the first ("your sexual desire is decreased?") – however, there is no mention of how the instrument was translated into Portuguese.

Thus, we adapted translations already used in research, specifically, a mixture of the translation used by Cabral (2012) and Blaya (2015). The adaption of both translations was necessary due to drastic divergences in comparison to the original; for example, the original question 4 is about the loss of height related to osteoporosis, which is a symptom of hypogonadism (MORLEY et al., 2000), while in the version used by Cabral, question 4 is about weight loss (CABRAL, 2012). Originally, question 8 was about the ability to play sports (MORLEY et al., 2000). However, in the questionnaire used by Blaya (2015), question 8 is about the ability to maintain an erection during sexual intercourse. Therefore, to be as close as possible to the original, we kept question number eight on sports practice and question number four on height loss.

4.6.7. Bloodwork

This study included bloodwork to evaluate hypogonadism, metabolic syndrome, and cardiovascular risk estimation. We measured glucose, total cholesterol, triglycerides, high-density cholesterol (HDL), low-density cholesterol, non-HDL cholesterol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and total testosterone (TT) using standardized methods and chemiluminescence for the TT analysis. Bloodwork was performed in a reference Laboratory of the Federal District. Due to the glucose and testosterone measurements, volunteers were instructed to fast between 8-12 hours, get the bloodwork done before 10 AM, remain 24h without alcohol and physical exertion, and wait for at least 48h after working a 24h shift. Also, they were instructed to postpone the exam in case of excessive stress or a bad night's sleep. As for the second measurement, the instructions were the same as the first one. Whenever possible, exams were separated by a minimum of 7 days. The median difference was 16 days (11 days, 29 days). This time difference happened because of the time necessary to get in touch with the volunteer after the results were made available by the lab while respecting their personal agenda. For example, some volunteers performed the bloodwork before traveling on vacation, so it was necessary to wait for their return to do the second measurement. Others had more difficulties scheduling bloodwork due to intense work schedules and the strict study procedures before bloodwork.

4.6.8. Hypogonadism definition

Volunteers were classified as having hypogonadism when they had low TT confirmed by two different blood samples and presented signs and symptoms per Endocrine Society guidelines (BHASIN et al., 2018). Low testosterone was defined as values lower than 320 ng/dL in both measurements – approximately the 10th percentile of a harmonized normal range of European and American men (BHASIN et al., 2018; TRAVISON et al., 2017) and the recommended cut-off point to be associated with symptoms by the European Male Aging Study data (BHASIN et al., 2018; WU et al., 2010). A participant having an ADAM+ was considered as presenting signs and symptoms of hypogonadism. Exceptionally, we also included FF who were unable to perform a second TT measurement and had a very low TT – less than 264 ng/dL, the 2.5th percentile of a harmonized normal range of European and American men (BHASIN et al., 2018; TRAVISON et al., 2017). This was the case for five FFs, all having ADAM+, indicating we had made a reasonable methodological choice. For these individuals, TT values ranged between 133.7-260.9 ng/dL. These individuals did not do the second measurement because of lack of time (40%), illness (20%), and COVID outbreak (40%). Of note, none of the other volunteers who performed two TT measurements and had the first one < 264 ng/dL plus ADAM+ had the second measurement above 320 ng/dL, confirming the adequacy of our methodological decision.

Also, we included a subclinical hypogonadism group composed of FFs with confirmed low testosterone (<320 ng/dL) in both measurements but without signs and symptoms (ADAM-). It is crucial to investigate this group because they may develop signs and symptoms in the future and require treatment. Also, they may be at greater cardiovascular risk simply due to having confirmed low testosterone. Lastly, we also investigated another subgroup that we called the “borderline hypogonadism group.” This group was composed of individuals with a borderline-to-normal TT value – 320-399 ng/dL (BHASIN et al., 2018) - in the first measurement but had a very low second measurement (<264 ng/dL), with signs and symptoms (ADAM+).

4.6.3. Obesity definition

Obesity was defined as a BMI ≥ 30.0 kg/m². Initially, we were interested in different measurements of abdominal obesity, including waist circumference and waist-to-height ratio. However, since the 2021/2022 part of the study required only self-reported measurements, we decided not to include waist circumference since the validity of the self-report of such a measure is unknown.

4.6.4. Metabolic Syndrome definition

Metabolic syndrome classification followed the Joint Scientific Statement criteria (ALBERTI et al., 2009). A participant was classified as having metabolic syndrome if he presented three or more of the following risk factors:

- Reduced HDL-cholesterol (<40 mg/dl);
- Elevated triglycerides (>150 mg/dL) or use of triglyceride-lowering medication;
- Elevated blood pressure (systolic ≥130, diastolic ≥85 mmHg, or both), diagnosis of hypertension or antihypertensive drug treatment;
- Hyperglycemia (blood glucose ≥100 mg/dl), self-reported diagnosis of diabetes or antidiabetic drug treatment;
- Abdominal obesity.

Due to the unavailability of the waist circumference, we utilized BMI ≥30 kg/m² as a proxy for abdominal obesity (BAUR; CHRISTOPHI; KALES, 2012).

4.6.5. Cardiovascular risk

We used the Framingham risk score (FRS) to assess cardiovascular risk. The FRS is recommended by the *Sociedade Brasileira de Cardiologia* - Brazilian Cardiology Society (SBC) to assess global cardiovascular risk (PRÉCOMA et al., 2019). When calculating the FRS, recent quitters (≤ 6 months) were considered smokers. Risk score classification followed SBC's criteria, considering what we had available in our data:

- Low risk: FRS < 5%
- Moderate risk: FRS between 5 and 20%. People with diabetes without risk factors and FRS ≤ 20%.
- High risk: FRS > 20%. Men with LDL cholesterol ≥ 190 mg/dL.
- Very high risk: Self-reported episode or diagnosis of arrhythmia, myocardial infarction, coronary heart disease, or cerebral vascular disease.

4.6.5. Prevalence of cardiometabolic risk factors

To evaluate the prevalence of hypertension, we followed the definitions from *Sociedade Brasileira de Cardiologia (SBC)* (BARROSO et al., 2021):

- Hypertension: systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. We also included those using antihypertensive drug medication and self-reported hypertension.
- Pre-hypertension: SBP between 130-139 mmHg or DBP between 85-89 mmHg.
- Normal blood pressure: SBP ≤129 mmHg and DBP ≤84 mmHg.

We evaluated the prevalence of diabetes and hyperglycemia according to *Sociedade Brasileira de Diabetes (Brazilian Society of Diabetes)* (COBAS et al., 2021) and metabolic syndrome criteria (ALBERTI et al., 2009):

- Pre-diabetes: Fasting glucose ≥ 100 mg/dL or use of antihyperglicemic medication.
- Diabetes: Fasting glucose ≥ 126 mg/dL, self-reported diabetes or insulin use.

Lipids were evaluated according to the *Sociedade Brasileira de Cardiologia (SBC)* guidelines (PRÉCOMA et al., 2019):

- High total cholesterol: Total cholesterol ≥ 190 mg/dL

- Low HDL-C: HDL-C < 40 mg/dL
- High triglycerides: Triglycerides ≥ 150
- Excess LDL-C: LDL-C above cut-point according to cardiovascular risk (≥50 mg/dL for very high risk, ≥70 mg/dL for high risk, ≥100 mg/dL for intermediate risk, ≥130 mg/dL for low risk)
- Excess N-HDL-C: N-HDL-C above cut-point according to cardiovascular risk (≥80 mg/dL for very high risk, ≥100 mg/dL for high risk, ≥130 mg/dL for intermediate risk, ≥160 mg/dL for low risk)

4.7. RESPONSE RATE

During the 2020 part of the study, the research team personally invited FFs to participate while on duty in various parts of the Federal District of Brazil. A total of 47 FFs were invited to participate, with the most accepting the invitation (n=33; 70.2%). Also, a total of 8 FF had retired before we made contact. Similarly, when we received the names and workplaces of the FFs, we found out one was female. The main reasons for not participating were lack of time or interest.

Throughout the 2021/2022 part of the study, we requested data for a total of 1,048 FFs to be reached through text messages or calling the unit they are serving in. This was necessary due to a low response rate and some FFs being immediately excluded as soon as researchers received data. Specifically: 2 FFs had passed away, 60 FFs already had retired, 3 were women who performed the male fitness test, 1 FF was not identified through his registration number (passed away or fired), 4 FFs were confirmed to be working outside the CBMDF; thus, no attempt was made to get in touch with them. Of the remaining 978 FFs, 74 FFs did not have a cellphone number or did not have Whatsapp. Of the 904 FFs we attempted to reach through Whatsapp, 375 accepted to participate, with 326 completing the questionnaire. Reasons for not completing were not given since only two volunteers stated they did not wish to participate anymore, while the others stopped replying. Regarding the 527 FFs who did not participate, only 155 responded to the researchers and refused to participate or were excluded for the following reasons: 50 for having retired, 43 declared they were not interested or did not have a specific reason, 28 for working outside the Fire Service, 12 for personal reasons (e.g., family issues), 9 due to time constraints, 7 did not want to perform bloodwork or share personal data, 3 due to health issues participating, 2 for testosterone usage, 1 was already participating in another research involving testosterone usage.

4.8 DATA PROCESSING

Volunteers responded to an online questionnaire that automatically created a spreadsheet with their answers. Using Microsoft Excel, text answers were converted to numbers for statistical analysis. Bloodwork results were obtained online using the Laboratory system. Due to the nature of the survey software, questions that would normally require a short, number-only answer sometimes were allowed to have complete phrases written. In some cases, volunteers added margins or extra information to the answer. For example, for the question, “How much time, in minutes, do you take to sleep”? There were answers like “between 10-15 minutes”, “up to 10 minutes”, and “a maximum of 30 minutes”. For the first type of answer, we used the average between the two mentioned numbers; in the first example, data would be input as 12.5 minutes. Following the same logic, we would consider the lower number zero in the other two examples. This way, the data input for the other two examples would be “5” and “15” minutes, respectively. When a volunteer answered that he slept “immediately,” the answer was coded as one minute since this was the smallest value reported in our sample. In a question about smoking, to assess for cardiovascular risk, we also considered “vaping” as smoking.

When answering the International Physical Activity Questionnaire (IPAQ), one volunteer did not clearly answer his walking time, and another his moderate PA time. We did not successfully get a return from them to clarify this, and we decided not to include them in the total moderate-to-vigorous minutes' comparison. Still, they were included in the categorical analysis because they were obviously active when examining other components of PA.

4.9 STATISTICAL METHODS

Data normality was evaluated using the Kolmogorov-Smirnov test, histogram, and Q-Q plots visual inspection (GHASEMI; ZAHEDIASL, 2012). Most variables did not present a normal distribution, which could result from the large sample size (higher falsepositive rates in normality tests). Further visual inspection of the histograms and Q-Q plots indicated that this probably resulted from "enriching" two groups, the high-risk and low-risk FFs. Most variables presented two peaks and slight skewness due to the criteria for creating those groups. We decided to use a non-parametric approach to describe and analyze data.

Continuous data are presented as median (1st quartile; 3rd quartile) and categorical as the number of cases and percent. The Mann–Whitney U and Kruskal-Wallis tests were used to compare differences between two or three groups. Dunn's post-hoc analysis was used in case of a significant difference in the Kruskal-Wallis test. Association between variables was analyzed using chi-square tests, with crude and adjusted odds ratios (OR) with 95% confidence intervals (95%CI) calculated to express the strength of the association. Most of the analyses were adjusted only based on age due to BMI being a criterion for MS and Ob. Due to the non-parametric distribution, we utilized a generalized linear model analysis based on the gamma distribution to analyze continuous predictors and, when necessary, for age- and BMI-adjusted analysis. This type of analysis is more robust than standard linear regression and an alternative to data transformation (BARBER et al., 2004; KILIAN et al., 2002). To better compare the characteristics of FF with LOH, we created a "true" reference group composed of volunteers without any signs or symptoms related to LOH (ADAM-) and with TT levels that are "undoubtedly" normal (≥ 400 ng/dL) per Endocrine Society (BHASIN et al., 2018).

The IBM SPSS Statistics® 21 (IBM Corporation, USA) software package was used for data processing and analysis, and Prism 8 for Windows (GraphPad Software, USA) for graphic design. A two-tailed P-value of less than 5% (0.05) was considered a statistically significant difference.

4.9.1. Statistical analysis

In a continuous analysis involving serum TT levels, we chose the value of the second measurement to represent serum TT measurements in FFs with two dosages. This decision was based on a clinical viewpoint that usually the second measurement represents better, and volunteers "prepared better" for the second one due to a possible alteration in the first.

We compared the high-risk, low-risk, and neutral-risk groups to confirm that our selection process resulted in groups with significantly different TT values. This analysis is presented as “preliminary results” in the “results” section. To attend to our first aim, we calculated the prevalence and 95% confidence interval (CI) of hypogonadism, metabolic syndrome, and obesity in Brazilian FFs. We employed inverse probability weighting to estimate the three prevalence and 95% CI for the entire Fire Service (study sample unweighted, which corresponds to the population estimates). To evaluate associate factors with this prevalence, we performed a logistic regression, first in a bivariate analysis, to construct a more extensive model retaining variables with an association with $p < 0.2$, which was used in the second analysis.

As our secondary aims, we explored the prevalence of different forms of classifying individuals with low testosterone presenting symptoms or not using by estimating population prevalence and 95%CI. We also investigated the association between LOH and other forms of classifying LOH and low TT with MS and Ob. We compared the characteristics of groups with LOH vs. without LOH, with MS vs. without MS characteristics, and Ob vs. without Ob.

Lastly, we performed an exploratory analysis, presenting serum TT levels as a continuous variable and associating it with age, BMI, CRF, and estimated VO_2max. The Spearman correlation was used to express the strength of the association. We also compared characteristics between groups composed based on TT levels. Criteria were based on previous research on FF (LOFRANO-PORTO et al., 2020; RANADIVE et al., 2021), the Endocrine Society Guideline (BHASIN et al., 2018), and TT normative values (TRAVISON et al., 2017). Groups were based on the following levels: <264 ng/dL, 264-319 ng/dL, 320-399 ng/dL, 400-916 ng/dL, and >916 ng/dL. The last group was mainly described but not included in all analyses due to the small number of individuals (n=5). A generalized linear model regression was also performed to investigate possible predictors of TT values.

4.9.2. Inverse probability weighting

To account for the enriched randomization process in our prevalence estimates, we utilized inverse probability weighting (IPW). Briefly, since we oversampled FFs classified as having a high risk for hypogonadism in our research design, it is necessary to correct this oversampling to calculate a representative sample for the Fire Service (MANSOURNIA; ALTMAN, 2016). It is necessary to apply a weight to each related to the group they are assigned to in order to perform this correction, e.g., a group whose proportion in a sample is double the proportion in a population receives a weight of 0.5. Similarly, a group whose proportion in a sample is half the proportion in a population gets a weight of 2.0. Weights can be interpreted as the number of members from a specific population the survey respondent represents (GATS, 2010). Thus, using IPW, a sample weight applied to an individual is the inverse probability of his selection (MANSOURNIA; ALTMAN, 2016). It is common to weigh individuals based on the study design weights; however, we opted to use a post-data collection weight based on the ratio between the probability of an individual being selected in the population and the probability of being selected in the sample (HERNAN; ROBINS, 2022). We used this approach due to access to the original population data and the lower proportion of high-risk individuals compared to the sample design. Since data from the 2019 fitness test and 2021 had a slightly different number of FFs, we calculated weights for FF whose fitness test was from 2019 using the respective years' data. Using sample data, the high-risk and low-risk groups were oversampled compared to the population, having a proportion of 3.2 and 1.2 times greater. The neutral-risk group was undersampled, with a proportion in the sample 0.5 times lower than the population proportion. Weight data from 2021 and 2019 were identical when rounded to the first decimal. Using IPW, the weights of the high-risk, low-risk, and neutral-risk groups were 0.3, 0.8, and 2.0, respectively.

5. RESULTS

Considering the high number of variables and analyses, the results will be presented in subtopics as follows:

5.1 – Data related to preliminary analyses regarding the sample and the impact of the enriched randomization strategy, as well as the demographic characteristics of the sample;

5.2 – Data regarding the prevalence estimates of LOH, MS, and obesity (the primary goal of the study, as well as secondary goal number 3.2.1);

5.3 – Data regarding a possible association between the investigated outcomes (LOH, MS, and obesity) and cardiometabolic risk factors (secondary goals number 3.2.2 and 3.2.3);

5.4 – Data related to the association between serum TT levels and cardiometabolic risk factors, fitness, and quality of life (secondary goals number 3.2.4 and 3.2.5);

5.5 – Data regarding logarithmic regression models to investigate predictors of LOH, MS, and obesity within those male military career firefighters (secondary goal number 3.2.6).

5.1. PRELIMINARY RESULTS REGARDING THE SAMPLE

We utilized a cross-sectional design to investigate the prevalence of male hypogonadism, metabolic syndrome, and obesity in Brasília's FFs. To achieve a reasonable number of participants with hypogonadism, we utilized an enriched randomization sampling strategy using age, BMI, and cardiorespiratory fitness tests' results. We classified FFs as having a high risk, or not, for hypogonadism. We proceeded in the same manner to form a low-risk group. Lastly, a neutral-risk group was composed of FFs who did not fit into either category.

We compared the main variables and cardiovascular risk factors to confirm our hypothesis that the different groups would present different serum TT levels and cardiovascular risk factors (Table 1). Prevalence of hypogonadism, metabolic syndrome (MS), and obesity were, respectively, 18.3%, 66.4%, 100% for the high-risk group, 0.9%, 12.3%, 6.6% for the neutral risk group, 1.1%, 3.3%, 0% for the low-risk group. Results from normality tests performed in the data were mainly significant ($p < 0.05$), pointing to a non-normal distribution in the variables. Examining the data distribution, we interpreted that the significant differences between groups led to skewed data, sometimes leptokurtic. Even when analyzing the whole sample, the effect of combining very different groups was seen, with some data presenting bimodal characteristics, with “two peaks.” For example, the high-risk group had a minimum BMI of 30.0 kg/m², while the low-risk group had a maximum BMI of 29.9 kg/m². However, the age restriction in this group possibly contributed to a concentration of values around 25 kg/m², with 50% of this group having values between 24-26 kg/m² (Table 1). These observations strengthened our decision to opt for a non-parametric analysis. The characteristics of our sample, including the unweighted data, are shown in table 2.

Table 1: Comparison of serum total testosterone, fitness, and cardiovascular risk variables (median [Q1, Q3]) by risk-for-hypogonadism groups among male firefighters (n = 328)

	High-risk group (n=131)	Neutral-risk group (n=106)	Low-risk group (n=91)	p
Serum TT (ng/dL)	426.0 (294.5; 507.9)[a,b]	476.2 (421.8; 577.0)[b]	550.5 (475.1;682.0)	<0.01
Age (years)	47.8 (45.2; 49.2)[a,b]	44.7 (35.3; 48.3)[b]	32.6 (30.5; 35.1)	<0.01
BMI (kg/m^2)	32.1 (30.9; 34.0)[a,b]	28.3 (25.8; 29.4)[b]	25.1 (23.7; 26.4)	<0.01
SBP (mmHg)	130 (120;140)[b]	127 (120; 130)[b]	120 (118;129)	<0.01
DBP (mmHg)	85 (80; 90)[b]	81 (80; 89)[b]	80 (73; 82)	<0.01
FRS (%)	9.2 (6.5; 11.7)[a,b]	5.9 (3.0; 8.5)[b]	1.9 (1.4; 2.7)	<0.01
VO_2max (mL/kg/min)	28.7 (25.3; 33.6)[a,b]	38.3 (32.7; 41.9)[b]	44.3 (41.6; 48.2)	<0.01

TT: total testosterone; BMI: body mass index; SBP: systolic blood pressure; FRS: Framingham risk score; p: non-parametric ANOVA p-value; [a]: Significantly different from the neutral-risk group; [b]: Significantly different from the low-risk group.

Table 2: Demographic characteristics of the sample

	Study sample (n=328)	Study sample unweighted
Age (years)	43.6 (33.6; 48.1)	41.2 (32.8; 47.5)
BMI (kg/m²)	29.4 (25.7; 31.6)	27.8 (25.3; 29.6)
Systolic BP (mmHg)	127 (120; 131)	126 (120; 130)
Diastolic BP (mmHg)	80 (80; 89)	80 (79; 88)
Hypertension - categories - n (%)*		
Pre-hypertension (SBP: 130-139 or DBP: 85-89 mmHg)	69 (21.0)	71 (21.7)
Hypertension (SBP: >= 140 or DBP >= 90 mmHg or medicated)	115 (35.1)	103 (31.4)
Glucose (mg/dL)	90 (85; 94)	89.0 (85; 94)
Glucose – categories – n (%)#		
prediabetes (100 – 125 mg/dL or medicated)	42 (12.8)	30 (9.3)
diabetes (≥ 126 mg/dL or self-reported)	8 (2.4)	4 (1.2)
Serum total testosterone (ng/dL)	472.9 (398.8; 576.1)	487.6 (419.5; 588.7)
Positive ADAM questionnaire – n (%)	197 (60.1%)	189 (57.8%)
Framingham risk score (%)	5.7 (2.4; 9.5)	4.6 (2.3; 8.0)
VO_2max (mg/kg/min)	36.7 (29.5; 42.7)	39.6 (32.8; 43.7)
Unfit (<12 METs) – n (%)	232 (70.7)	217 (66.3)
Total MVPA weekly minutes (n=325)	425 (180; 795)	450 (220; 812)
MVPA <150 minutes – n (%)	67 (20.6%)	60 (18.3%)
Quality of Life		
Physical domain	71.4 (60.7; 78.6)	75.0 (64.3; 82.1)
Psychological domain	70.8 (62.5; 79.2)	70.8 (62.5; 79.2)
Social domain	75.0 (58.3; 75.0)	75.0 (58.3; 75.0)
Environmental domain	68.8 (60.2; 75.0)	68.8 (62.5; 76.1)
PSQI (no unit)	6 (4; 9)	6 (4; 9)
Poor sleep quality (PSQI >5)	183 (55.8)	193 (59.2)

Continuous variables are expressed as median (1st quartile; 3rd quartile). BMI: body mass index; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; ADAM: Androgen deficiency in the aging male. MVPA: Moderate-to-vigorous physical activity; PSQI: Pittsburgh sleep quality index.; *: 2021 – Sociedade Brasileira de Cardiologia; #: 2020-American Diabetes Association

5.2 PREVALENCE DATA

Due to the enriched randomization, we will report the sample prevalence and the "unweighted" prevalence, which represents the studied population accurately. We observed a sample late-onset hypogonadism (LOH) prevalence of 7.9%. The sample's metabolic syndrome (MS) prevalence was 31.4%, while obesity (Ob) was 42.1%. The prevalence estimates for the population (unweighted values) were: 3.2%, 17.0%, and 16.9%, respectively. Figure 3 presents sample and unweighted data, with their respective 95%CI.

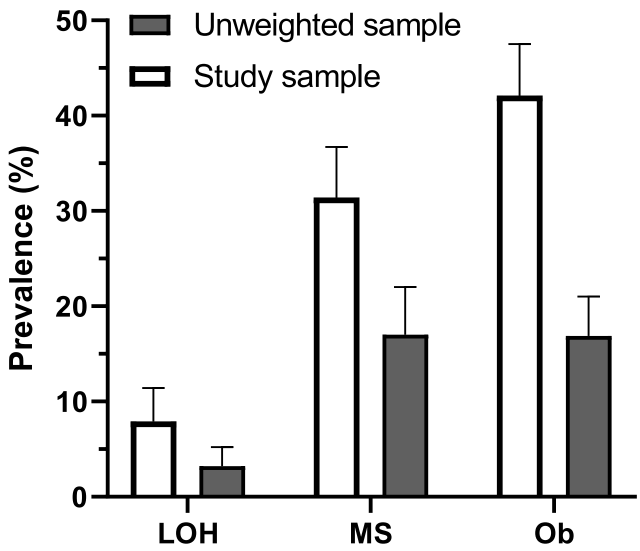

Figure 3: Late-onset hypogonadism (LOH), metabolic syndrome (MS), and obesity (Ob) prevalence data.

To highlight the importance of classifying hypogonadism as both symptoms and low-testosterone levels, we also compared different prevalence rates in the unweighted study sample (population estimates) using two criteria for LOH and other conditions associated with low TT, as shown in Table 3. Of note, the hypogonadism criterion is the gold standard.

Table 3: Estimated population prevalence of hypogonadism and low testosterone using various criteria

Group	Blood criteria	Signs and symptoms	Prevalence (95%CI)
Hypogonadism	2x TT <320 ng/dL, or 1x TT<264 ng/dL for FFs without 2 measurements	ADAM+	3.2% (1.9-5.2%)
Subclinical Hypogonadism	2x TT <320 ng/dL	ADAM-	2.1% (0.9-4.9%)
Borderline hypogonadism	1st TT between 320-399 ng/dL, 2nd <264 ng/dL.	ADAM+	2.6% (1.1-5.9%)
Hypogonadism, but only the 1st measurement	1st TT <320 ng/dL	ADAM+	7.1% (4.6-10.9%)
Low testosterone	2x TT <320 ng/dL, or 1x TT<264 ng/dL for FFs without 2 measurements	ADAM+ or ADAM-	5.3% (3.4-8.3%)
Low testosterone, but only the 1st measurement	1st TT <320 ng/dL	ADAM+ or ADAM-	14.9% (10.9-20.0%)

TT: Total testosterone; ADAM+: Considered positive for Androgen Deficiency in the Aging Male Questionnaire (ADAM); ADAM-: Considered negative for the ADAM questionnaire; CI: Confidence interval.

5.2.1 Serum TT values and associations

Serum TT values may vary across age ranges and between men with and without obesity. Since FFs are a specific population, it is interesting to investigate if the distribution varies between other representative cohorts. Table 4 presents the distribution of TT across the sample using various percentiles.

Table 4: Distribution of total serum testosterone (ng/dL) levels in the study sample, subgroups, and unweighted sample

	Percentiles								
	2.5	5.0	10.0	25.0	50.0	75.0	90.0	95.0	97.5
Sample unweighted	233	261	306	420	488	589	710	756	852

The characteristics of FFs with different testosterone levels are presented in Table 5. Because the high testosterone group (>916 ng/dL) was composed of only five FFs, they are described in the table but were not included in the analysis.

Table 5: Comparison of serum total testosterone, fitness, and cardiovascular risk variables (median [Q1, Q3]) between male FF with different testosterone levels (n = 328)

	<320 ng/dL (n=55)	320-399 ng/dL (n=29)	400-916 ng/dL (n=239)	p	>916 ng/dL (n=5)
Serum TT (ng/dL)	252.9 (230.8; 294.2)[b]	353.7 (334.7; 386.3)[b]	519.6 (457.0; 600.1)	<0.01	1013.9 (962.4; 1222.3)
Age (years)	47.7 (41.7; 49.3)[b]	46.0 (33.9; 47.8)	41.2 (32.8; 47.9)	<0.01	36.8 (29.7; 37.7)
BMI (kg/m^2)	32.1 (29.9; 34.3)[a,b]	30.1 (27.0; 31.5)	28.4 (25.5; 30.8)	<0.01	24.0 (22.2; 25.7)
SBP (mmHg)	130 (122; 140)[b]	129 (120;130)	125 (120;131)	0.01	120 (112;126)
DBP (mmHg)	88 (80; 90)[b]	80 (80; 88)	80 (78; 88)	<0.01	77 (65; 81)
FRS (%)	9.6 (7.0; 12.3)[a,b]	6.5 (2.9; 9.7)	4.4 (2.2; 8.0)	<0.01	2.0 (1.6; 3.3)
VO_2max (mL/kg/min)	29.7 (24.7; 34.7)[b]	35.3 (30.3; 40.9)	38.3 (31.6; 44.2)	<0.01	44.3 (43.5; 48.9)
MVPA weekly minutes*	330 (100; 535)	460 (170; 803)	440 (198; 815)	0.16	1200 (546; 1790)
QoL - Physical	67.9 (57.1; 78.6)[b]	67.9 (50.0; 76.8)	75.0 (64.3; 82.1)	0.01	82.1 (73.2; 92.9)
QoL - Psychological	70.8 (58.3; 79.2)	66.7 (58.3; 75.0)	75.0 (62.5; 79.2)	0.05	75.0 (70.8; 83.3)
QoL - Social	66.7 (50.0; 75.0)	66.7 (50.0; 75.0)	75.0 (58.3; 75.0)	0.20	75.0 (58.3; 75.0)
QoL- Environmental	68.8 (59.4; 71.9)	65.6 (54.7; 75.0)	68.8 (62.5; 75.0)	0.32	75.0 (71.9; 92.2)
PSQI	6 (4; 9)	6 (4; 11)	6 (4; 9)	0.58	7 (5; 8)
Glucose (mg/dL)	90 (84; 99)	91 (86; 95)	89 (85; 94)	0.23	82 (79; 89)
TC (mg/dL)	188 (164; 221)	185 (151; 215)	188 (161; 214)	0.43	195 (168; 205)
Triglycerides (mg/dL)	159 (119; 241)[b]	119 (83; 183)	107 (76; 154)	<0.01	85 (55; 101)
HDL-C (mg/dL)	40 (34; 46)[b]	42 (35; 50)	45 (40; 53)	<0.01	55 (52; 60)
LDL-C (mg/dL)	125 (95; 150)	113 (88; 141)	119 (97; 146)	0.47	122 (100; 140)
Non-HDL-C	144 (120; 180)	135 (105; 172)	142 (116; 164)	0.15	143 (110; 149)
LH (mIU/mL)	2.73 (1.72; 3.31)[b]	3.53 (2.24; 4.68)	3.68 (2.73; 4.49)	<0.01	3.76 (1.85; 5.55)
FSH (mIU/mL)	2.9 (2.0; 4.4)	3.4 (1.9; 5.2)	3.3 (2.3; 4.6)	0.35	3.0 (1.5; 3.7)

TT: total testosterone; BMI: body mass index; SBP: systolic blood pressure; FRS: Framingham risk score; MVPA: Moderate-to-vigorous physical activity; QoL: Quality of Life – no unit; PSQI: Pittsburgh sleep quality index - no unit; *p: Kruskal-Wallis test p-value; [a]: Significantly different from the 320-399 ng/dL group; [b]: Significantly different from the 400-916 ng/dL group.

We also examined how TT varied between the first and second dosages. There was a significant difference between both dosages (13.3 ng/dL [-27.9 ng/dL, 74.0 ng/dL]; p=0.04), ranging from a decrease of 222 ng/dL to an increase of 153 ng/dL. Exceptionally, one FF increased 413 ng/dL at the second measurement. He was a young triathlete under severe training while preparing for a competition, and the 24h rest requested by the study was insufficient. Due to time constraints, he performed the second measurement 72 hours after the first one and rested for approximately 60 hours. His TT went from 131.4 ng/dL to 544.8 ng/dL. TT decrease ranged from 222 to 1 ng/dL (46% of cases) while the increase ranged from 8 to 153 ng/dL (54% of cases) – not including the exceptional 413 ng/dL increase. Regarding the classification of TT levels, out of the 88 FFs who performed a second TT measurement, only 32 (36.4%) did not change their category.

Table 6: Comparison between total testosterone (TT) categories in the first and second measurement

	2nd TT (ng/dL)			
1st TT (ng/dL)	<264	264-319	320-399	400-916
<264	11 (41%) **(61%)**	6 (35%) **(33%)**	0 (0%) **(0%)**	1 (5%) **(6%)**
264-319	8 (30%) **(30%)**	6 (35%) **(22%)**	9 (38%) **(33%)**	4 (20%) **(15%)**
320-399	8 (30%) **(18%)**	5 (29%) **(12%)**	15 (63%) **(35%)**	15 (75%) **(35%)**
400-916	0 (0%) **(0%)**	0 (0%) **(0%)**	0 (0%) **(0%)**	0 (0%) **(0%)**

Bold values represent line percentages, and non-bold are column percentages.

5.3 OUTCOME ASSOCIATION ANALYSES

To explore the relationship between LOH, MS, and obesity, we analyzed the prevalence of LOH and MS in the different BMI categories. We also analyzed subclinical LOH and borderline LOH to explore a possible association with BMI. Figures 4 and 5 present the estimated population prevalence of LOH and MS in the different BMI categories. The figures also include a reference group and a group called "rest of the sample" that consists of all other cases that do not fit in any of the above categories.

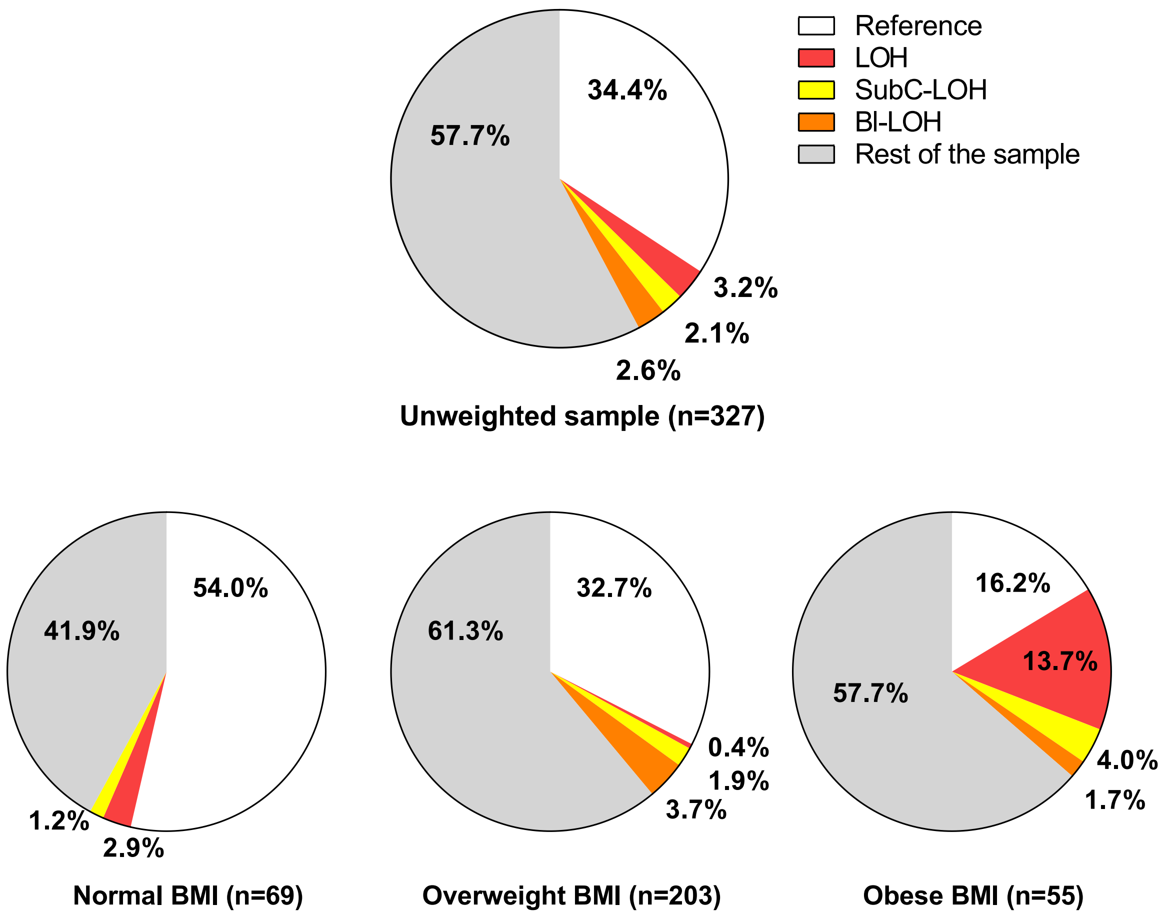

Figure 4: Estimated population prevalence of late-onset hypogonadism (LOH), subclinical hypogonadism (SubC-LOH), borderline hypogonadism (Bl-LOH) in body mass index (BMI) categories, reference group (serum TT ≥ 400 ng/dL; ADAM-).

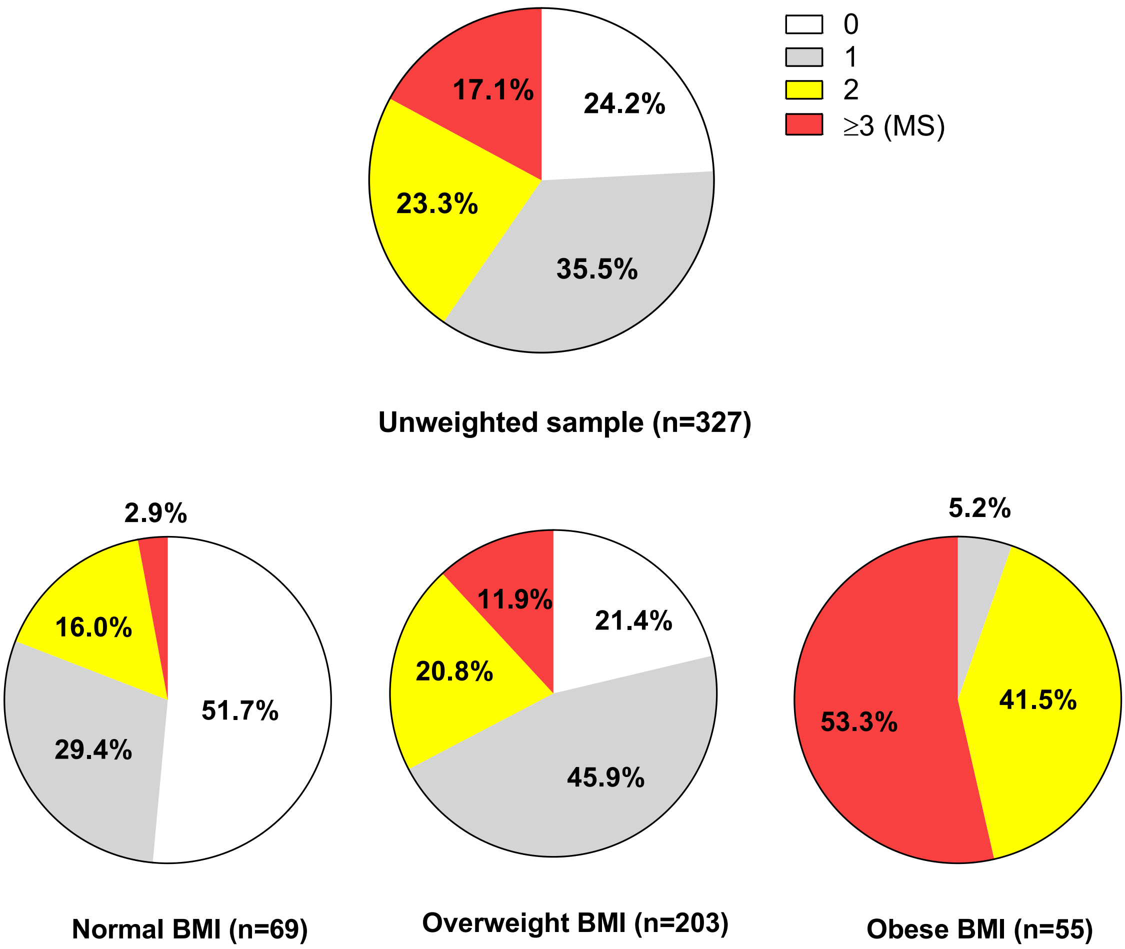

Figure 5: Estimated population prevalence of zero, one, two, three, or more metabolic abnormalities in different BMI categories. Three or more abnormalities are equivalent to attending the metabolic syndrome (MS) criteria.

Within the MS group, the most prevalent risk factor was elevated blood pressure (86.4%), followed by obesity (85.4%), elevated triglycerides (77.7%), reduced HDL-cholesterol (61.2%), and hyperglycemia (36.9%). Those proportions in the study sample were 61.9%, 42.1%, 33.5%, 29.0%, and 14.3%, respectively.

Also, we explored the association between MS or obesity and different ways to classify hypogonadism and low testosterone to show the importance of having both symptoms and de-facto low testosterone. Tables 6 and 7 also include an age-adjusted analysis. In the MS analysis, BMI was not used since it is an MS criterion.

Table 6: Odds ratio of having metabolic syndrome in male firefighters with hypogonadism and various TT levels and symptoms classification compared to those with TT in the reference range and without any hypogonadism symptoms.

			Crude analysis		Adjusted analysis#	
Group	n	%	OR (95%CI)	p	OR (95%CI)	p
Metabolic syndrome						
Reference group (TT ≥ 400 ng/dL; no symptoms)	103	16.5	1.00	-	1.00	-
Hypogonadism (ADAM+; TT < 320 ng/dL 2x, or 1st TT <264 ng/dL)	26	80.8	21.25* (7.04 – 64.17)	<0.01	11.53* (3.54 – 37.51)	<0.01
Subclinical Hypogonadism (ADAM-; TT < 320 ng/dL 2x)	10	60.0	7.59* (1.93 – 29.80)	<0.01	5.62 (1.31 – 24.10)	0.02
Borderline hypogonadism (ADAM+; 1st TT 320-399; 2nd TT <264 ng/dL)	8	25.0	1.69 (0.31 – 9.07)	0.54	0.90 (0.15 – 5.33)	0.91
Hypogonadism 1st (ADAM+; 1st TT < 320 ng/dL)	39	71.8	12.88* (5.39 – 30.74)	<0.01	8.24* (3.29 – 20.65)	<0.01
Low TT (TT < 320 ng/dL 2x, or 1st TT <264 ng/dL)	36	75.0	15.18* (6.07 – 37.94)	<0.01	9.00* (3.39 – 23.87)	<0.01
Low TT 1st (1st TT < 320 ng/dL)	69	60.9	7.87* (3.87 – 16.01)	<0.01	4.96* (2.32 – 10.60)	<0.01

TT: Total testosterone; ADAM+: Considered positive for Androgen Deficiency in the Aging Male Questionnaire (ADAM); ADAM-: Considered negative for the ADAM questionnaire; p: Pearson´s Chi-square p-value. #: Adjusted for age *= Significantly different compared to the reference group.

Table 7: Odds ratio of having obesity in male firefighters with hypogonadism and various TT levels and symptoms classification compared to those with TT in the reference range and without any hypogonadism symptoms.

			Crude analysis		Adjusted analysis#	
Group	n	%	OR (95%CI)	p	OR (95%CI)	p
Obesity						
Reference group (TT ≥ 400 ng/dL; no symptoms)	103	22.3	1.00	-	1.00	-
Hypogonadism (ADAM+; TT < 320 ng/dL 2x, or 1st TT <264 ng/dL)	26	92.3	41.74* (9.17 – 189.93)	<0.01	17.31* (3.40 – 88.04)	<0.01
Subclinical Hypogonadism (ADAM-; TT < 320 ng/dL 2x)	10	70.0	8.12* (1.94 – 33.91)	<0.01	6.65 (1.21 – 36.43)	0.03
Borderline hypogonadism (ADAM+; 1st TT 320-399; 2nd TT <264 ng/dL)	8	37.5	2.09 (0.46 – 9.40)	0.39	0.70 (0.13 – 3.84)	0.69
Hypogonadism 1st (ADAM+; 1st TT < 320 ng/dL)	39	82.1	15.90* (6.21 – 40.71)	<0.01	9.03* (3.21 – 25.43)	<0.01
Low TT (TT < 320 ng/dL 2x, or 1st TT <264 ng/dL)	36	86.1	21.57* (7.53 – 61.77)	<0.01	11.70* (3.56 – 38.46)	<0.01
Low TT 1st (1st TT < 320 ng/dL)	69	71.0	8.52* (4.25 – 17.11)	<0.01	4.87* (2.21 – 10.75)	<0.01

TT: Total testosterone; ADAM+: Considered positive for Androgen Deficiency in the Aging Male Questionnaire (ADAM); ADAM-: Considered negative for the ADAM questionnaire; p: Pearson´s Chi-square p-value. #: Adjusted for age *= Significantly different compared to the reference group.

We also investigated the association between cardiorespiratory fitness (CRF) and LOH, low TT, MS, and OB (Tables 8-11). Even though the proportion of LOH or other criteria for LOH or low TT were statistically similar between CRF categories, it is essential to note that almost all FFs with LOH (96.1%) showed CRF below 10 METs. On the other hand, 78,6% of those with CRF > 14 METs had TT in the reference range.

Table 8: Distribution of different clinical characteristics groups by various CRF levels

Groups	METs ≤10 (n=142)	10< METs ≤12 (n=96)	12< METs ≤14 (n=76)	METS >14 (n=14)	p-value	adj. p-value
Reference group (TT ≥ 400 ng/dL; no symptoms) (n=103)	25 (17.6) **(24.3)**	25 (26.0) **(24.3)**	42 (55.3) **(40.8)**	11 (78.6) **(10.7)**		
LOH (ADAM+; TT < 320 ng/dL 2x, or 1st TT <264 ng/dL) (n=26)	25 (17.6) **(96.2)**	0 (0.0) **(0.0)**	1 (1.3) **(3.8)**	0 (0.0) **(0.0)**	0.01	0.08
Subclinical Hypogonadism (ADAM-; TT < 320 ng/dL 2x) (n=10)	5 (3.5) **(50.0)**	2 (2.1) **(20.0)**	2 (2.6) **(20.0)**	1 (7.1) **(10.0)**	0.34	0.05
Borderline hypogonadism (ADAM+; 1st TT 320-399; 2nd TT <264 ng/dL) (n=8)	5 (3.5) **(62.5)**	2 (2.1) **(25.0)**	1 (1.3) **(12.5)**	0 (0.0) **(0.0)**	0.09	0.67
Rest of the sample (ADAM+ & ADAM-; TT 264-961 ng/dL) (n=181)	82 (57.7) **(45.3)**	67 (69.8) **(37.0)**	30 (39.5) **(16.6)**	2 (14.3) **(1.1)**		

LOH: Late-onset hypogonadism; MET: Metabolic equivalents; p-value: Chi-square test; Adj: Adjusted for age and BMI. Bold values represent line percentages, and non-bold are column percentages.

We observed a significant difference between TT levels and CRF, even when adjusted for age and BMI (Table 9) – lower testosterone levels were significantly associated with lower CRF levels. Interestingly, the proportion of FFs with low TT within the lower CRF category (≤10 METs) was 4.3-fold higher than the proportion within the higher CRF category (>14 METs). Also, among those with low TT, 78.2% had low CRF (≤10 METs), and only 10.9% had more than 12 METs.

Table 9: Distribution of different testosterone levels by various CRF levels

Testosterone levels n (%)	METs ≤10 (n=142)	10< METs ≤12 (n=96)	12< METs ≤14 (n=76)	METS >14 (n=14)	p-value	Adj. p-value
<320	43 (30.3) **(78.2)**	6 (6.3) **(10.9)**	5 (6.6) **(9.1)**	1 (7.1) **(1.8)**	<0.01	0.04
320-399	14 (9.9) **(48.3)**	13 (13.5) **(44.8)**	2 (2.6) **(6.9)**	0 (0.0) **(0.0)**		
400-916	85 (59.9) **(35.6)**	77 (80.2) **(32.2)**	65 (85.5) **(27.2)**	12 (85.7) **(5.0)**		
>916	0 (0.0) **(0.0)**	0 (0.0) **(0.0)**	4 (2.3) **(80.0)**	1 (7.1) **(20.0)**		

MET: Metabolic equivalents; p-value: Chi-square test; Adj: Adjusted for age and BMI. Bold values represent line percentages, and non-bold are column percentages.

Table 10 shows that the proportion of FFs with MS among those with CRF ≤12 METs was 14.5-fold higher than the group with CRF >12 METs. Also, no FF with CRF > 14 METs had MS. Similarly, 77% of the FFs with normal BMI had CRF >12 METs, while 78% of the FFs with obesity and a CRF <10 METs (Table 11). The distribution of CRF categories in the BMI categories was significantly different even when adjusted for age (p<0.01).

Table 10: Distribution of metabolic abnormalities by various CRF levels.

No. of metabolic abnormalities n (%)	METs C10 (n=142)	10< METs ≤12 (n=96)	12< METs ≤14 (n=76)	METS >14 (n=14)	p-value	Adj. p-value
0	2 (1.4) **(3.0)**	22 (22.9) **(32.8)**	33 (43.4) **(49.3)**	10 (71.4) **(14.9)**	<0.01	<0.01
1	16 (11.3) **(19.8)**	32 (33.3) **(39.5)**	29 (38.2) **(35.8)**	4 (28.6) **(4.9)**		
2	46 (32.4) **(59.7)**	21 (21.9) **(27.3)**	10 (13.2) **(13.0)**	0 (0.0) **(0.0)**		
≥3	78 (54.9) **(75.7)**	21 (21.9) **(20.4)**	4 (5.3) **(3.9)**	0 (0.0) **(0.0)**		

MET: Metabolic equivalents; p-value: Chi-square test; Adj: Adjusted for age. Bold values represent line percentages, and non-bold are column percentages.

Table 11: Distribution of normal, overweight, and obese BMI by various CRF levels

BMI category n (%)	METs ≤10 (n=142)	10< METs ≤12 (n=96)	12< METs ≤14 (n=76)	METS >14 (n=14)	p-value	Adj. p-value
Normal	2 (1.4) **(3.3)**	12 (12.5) **(20.0)**	32 (42.1) **(53.3)**	14 (100.0) **(23.3)**	<0.01	<0.01
Overweight	32 (22.5) **(24.6)**	55 (57.3) **(42.3)**	43 (56.6) **(33.1)**	0 (0.0) **(0.0)**		
Obese	108 (76.1) **(78.3)**	29 (30.2) **(21.0)**	1 (1.3) **(0.7)**	0 (0.0) **(0.0)**		

MET: Metabolic equivalents; p-value: Chi-square test; Adj: Adjusted for age. Bold values represent line percentages, and non-bold are column percentages.

Table 12 shows the odds of FFs having CRF below the NFPA recommended minimum value (12 METs) in LOH and low TT groups based on various criteria. Due to the strong influence of age and BMI, most associations lost significance when adjusted for these variables

Table 12: Odds ratio of having cardiorespiratory fitness under 12 METs in male firefighters with hypogonadism and various TT levels and symptoms classification compared to those with TT in the reference range and without any hypogonadism symptoms.

			Crude analysis		Adjusted analysis#	
Group	n	%	OR (95%CI)	p	OR (95%CI)	p
CRF <12 METs						
Reference group (TT ≥ 400 ng/dL; no symptoms)	103	48.5	1.00	-	1.00	-
Hypogonadism (ADAM+; TT < 320 ng/dL 2x, or 1st TT <264 ng/dL)	26	96.2	26.50* (3.46 – 202.94)	<0.01	1.69 (0.09 – 32.65)	0.73
Subclinical Hypogonadism (ADAM-; TT < 320 ng/dL 2x)	10	60.0	1.59 (0.42 – 5.97)	0.49	0.06* (0.01 – 0.66)	0.02
Borderline hypogonadism (ADAM+; 1st TT 320-399; 2nd TT <264 ng/dL)	8	87.5	7.42 (0.88 – 62.48)	0.07	1.68 (0.11 – 26.26)	0.71
Hypogonadism 1st (ADAM+; 1st TT < 320 ng/dL)	39	92.3	12.72* (3.69 – 43.94)	<0.01	1.27 (0.22 – 7.49)	0.79
Low TT (TT < 320 ng/dL 2x, or 1st TT <264 ng/dL)	36	86.1	6.57* (2.37 – 18.24)	<0.01	0.24 (0.04 – 1.61)	0.14
Low TT 1st (1st TT < 320 ng/dL)	69	87.0	7.07* (3.18 – 15.73)	<0.01	1.39 (0.42 – 4.60)	0.60

TT: Total testosterone; ADAM+: Considered positive for Androgen Deficiency in the Aging Male Questionnaire (ADAM); ADAM-: Considered negative for the ADAM questionnaire; p: Pearson´s Chi-square p-value. #: Adjusted for age and BMI *= Significantly different compared to the reference group.

Aiming to compare TT levels, fitness, and cardiovascular risk variables, we analyzed the characteristics between FFs with or without LOH, with or without MS, and with or without obesity. We also compared those variables between the LOH and TT reference groups. These comparisons are shown in Tables 13 to 16. Generally speaking, FFs with these conditions (LOH, MS, and Ob) were older, with higher BMI, and had lower testosterone and VO_2max in the crude and adjusted analysis.

Table 13: Comparison of serum total testosterone, fitness, and cardiovascular risk variables (median [Q1, Q3]) between male FF with late-onset hypogonadism characteristics and those without (n = 328)

	With LOH (n=26)	Without LOH (n=302)	p	P adj.*
Serum TT (ng/dL)	239.7 (227.0; 258.0)	484.9 (419.2; 585.9)	<0.01	<0.01
Age (years)	47.8 (46.1; 49.1)	41.7 (33.0; 48.0)	<0.01	N/A
BMI (kg/m^2)	33.5 (31.0; 36.2)	28.9 (25.5; 31.1)	<0.01	N/A
SBP (mmHg)	130 (126; 141)	126 (120;130)	0.01	0.22
DBP (mmHg)	90 (84; 93)	80 (79; 88)	<0.01	0.42
FRS (%)	10.9 (7.7; 13.0)	5.1 (2.3; 8.9)	<0.01	0.71
VO_2max (mL/kg/min)	25.4 (23.8; 30.6)	37.5 (31.2; 43.1)	<0.01	<0.01
MVPA weekly minutes	240 (30; 445)	440 (201; 828)	<0.01	0.03
QoL - Physical	64.3 (49.1; 75.9)	73.2 (64.3; 82.1)	0.02	0.27
QoL -Psychological	66.7 (54.2; 79.2)	70.8 (62.3; 79.2)	0.12	0.49
QoL – Social	66.7 (50.0; 75.0)	75.0 (58.3; 75.0)	0.11	0.44
QoL- Environmental	67.2 (59.4; 68.8)	68.8 (61.7; 75.0)	0.14	1.00
PSQI	9 (5; 11)	7 (5; 10)	0.71	0.81
Glucose (mg/dL)	92 (90; 101)	89 (85; 94)	0.05	0.40
TC (mg/dL)	194 (158; 227)	188 (161; 214)	0.49	0.68
Triglycerides (mg/dL)	184 (138; 229)	108 (77; 163)	<0.01	0.15
HDL-C (mg/dL)	40 (32; 45)	45 (39; 52)	<0.01	0.04
LDL-C (mg/dL)	133 (97; 163)	118 (96; 144)	0.35	0.84
Non-HDL-C	156 (120; 186)	142 (116; 165)	0.10	0.98
LH (mIU/mL)	2.65 (1.52; 3.25)	3.60 (2.56; 4.56)	<0.01	<0.01
FSH (mIU/mL)	2.5 (1.8; 4.0)	3.3 (2.2; 4.7)	0.05	<0.01

TT: total testosterone; BMI: body mass index; SBP: systolic blood pressure; FRS: Framingham risk score; MVPA: Moderate-to-vigorous physical activity; QoL: Quality of Life – no unit; PSQI: Pittsburgh sleep quality index – no unit; p: Mann-Whitney U test p-value; * Adjusted for age and BMI

Table 14: Comparison of serum total testosterone, fitness, and cardiovascular risk variables (median [Q1, Q3]) between male FF with late-onset hypogonadism characteristics and the reference group, FFs with no signs or symptoms of hypogonadism and total testosterone values greater-or-equal than 400 ng/dL (n = 129)

	With LOH (n=26)	Reference (n=103)	p	Adj. p
Serum TT (ng/dL)	239.7 (227.0; 258.0)	544.2 (463.5; 632.7)	<0.01	<0.01
Age (years)	47.8 (46.1; 49.1)	34.9 (31.0; 44.1)	<0.01	N/A
BMI (kg/m^2)	33.5 (31.0; 36.2)	26.5 (24.2; 29.4)	<0.01	N/A
SBP (mmHg)	130 (126; 141)	125 (119;130)	<0.01	0.34
DBP (mmHg)	90 (84; 93)	80 (74; 87)	<0.01	0.85
FRS (%)	10.9 (7.7; 13.0)	2.8 (1.6; 5.4)	<0.01	0.27
VO_2max (mL/kg/min)	25.4 (23.8; 30.6)	42.2 (35.6; 47.2)	<0.01	<0.01
MVPA weekly minutes	240 (30; 445)	405 (209; 919)	0.01	0.75
QoL - Physical	64.3 (49.1; 75.9)	78.6 (71.4; 85.7)	<0.01	<0.01
QoL -Psychological	66.7 (54.2; 79.2)	79.2 (70.8; 83.3)	<0.01	<0.01
QoL - Social	66.7 (50.0; 75.0)	75.0 (66.7; 83.3)	<0.01	<0.01
QoL- Environmental	67.2 (59.4; 68.8)	71.9 (68.8; 81.3)	<0.01	0.04
PSQI	6 (4; 10)	5 (3; 7)	0.71	<0.01
Glucose (mg/dL)	92 (90; 101)	88 (83; 93)	0.01	0.72
TC (mg/dL)	194 (158; 227)	188 (164; 211)	0.49	0.40
Triglycerides (mg/dL)	184 (138; 229)	90 (69; 125)	<0.01	<0.01
HDL-C (mg/dL)	40 (32; 45)	47 (42; 55)	<0.01	<0.01
LDL-C (mg/dL)	133 (97; 163)	117 (100; 145)	0.49	0.95
Non-HDL-C	156 (120; 186)	142 (114; 161)	0.05	0.94
LH (mIU/mL)	2.65 (1.52; 3.25)	3.95 (3.13; 4.95)	<0.01	<0.01
FSH (mIU/mL)	2.5 (1.8; 4.0)	3.3 (2.3; 4.5)	0.09	<0.01

TT: total testosterone; BMI: body mass index; SBP: systolic blood pressure; FRS: Framingham risk score; MVPA: Moderate-to-vigorous physical activity; QoL: Quality of Life – no unit; PSQI: Pittsburgh sleep quality index – no unit.; p: Mann-Whitney U test p-value; adj: age and BMI-adjusted p-value.

Table 15: Comparison of serum total testosterone, fitness, and cardiovascular risk variables (median [Q1, Q3]) between male FFs with and without metabolic syndrome characteristics (n = 328)

	Metabolic Syndrome (n=103)	No Metabolic Syndrome (n=225)	p	Adj. p
Serum TT (ng/dL)	417.2 (294.5; 477.0)	509.1 (432.6; 606.7)	<0.01	<0.01
Age (years)	47.3 (43.3; 49.0)	37.4 (32.2; 606.7)	<0.01	N/A
BMI (kg/m^2)	32.2 (30.7; 34.3)	27.2 (24.7; 29.8)	<0.01	<0.01
SBP (mmHg)	130 (123; 140)	124 (120;130)	<0.01	<0.01
DBP (mmHg)	85 (80; 90)	80 (78; 87)	<0.01	0.04
FRS (%)	9.8 (6.9; 12.3)	3.5 (1.9; 7.1)	<0.01	<0.01
VO_2max (mL/kg/min)	29.5 (25.3; 34.6)	40.2 (33.7; 44.8)	<0.01	<0.01
MVPA weekly minutes	320 (83; 568)	480 (260; 840)	0.01	0.23
QoL - Physical	67.9 (60.7; 78.6)	75.0 (64.3; 82.1)	<0.00	0.01
QoL -Psychological	70.8 (62.5; 79.2)	70.8 (62.5; 83.3)	0.10	0.06
QoL – Social	66.7 (58.2; 75.0)	75.0 (58.3; 75.0)	0.09	0.46
QoL- Environmental	65.6 (59.4; 75.0)	68.8 (62.5; 75.0)	0.02	0.66
PSQI	6 (4; 9)	6 (4; 9)	0.71	0.81
Glucose (mg/dL)	93 (88; 102)	88 (84; 92)	<0.01	<0.01
TC (mg/dL)	195 (165; 225)	183 (158; 211)	0.02	0.31
Triglycerides (mg/dL)	195 (151; 243)	94 (71; 124)	<0.01	<0.01
HDL-C (mg/dL)	38 (35; 44)	47 (42; 53)	<0.01	<0.01
LDL-C (mg/dL)	121 (95; 152)	117 (96; 143)	0.38	0.70
Non-HDL-C	156 (129; 184)	136 (113; 161)	<0.01	<0.01
LH (mIU/mL)	3.12 (2.35; 4.32)	3.68 (2.68; 4.49)	0.02	0.21
FSH (mIU/mL)	3.3 (2.4; 4.5)	3.1 (2.1; 4.7)	0.29	0.45

MS: Metabolic syndrome; TT: total testosterone; BMI: body mass index; SBP: systolic blood pressure; FRS: Framingham risk score; MVPA: Moderate-to-vigorous physical activity; QoL: Quality of Life – no unit; PSQI: Pittsburgh sleep quality index – no unit; p: Mann-Whitney U test p-value; adj: age-adjusted p-value.

Table 16: Comparison of serum total testosterone, fitness, and cardiovascular risk variables (median [Q1, Q3]) between male FF with and without obesity (n = 328)

	With obesity (n=138)	Without obesity (n=302)	p	Adj p
Serum TT (ng/dL)	426.0 (300.0; 504.8)	520.2 (436.5; 624.1)	<0.01	<0.01
Age (years)	47.6 (44.6; 49.1)	31.8 (35.8; 45.8)	<0.01	N/A
BMI (kg/m^2)	32.1 (30.9; 33.8)	26.3 (24.4; 28.4)	<0.01	<0.01
SBP (mmHg)	130 (120; 140)	125 (120;130)	<0.01	0.01
DBP (mmHg)	85 (80; 90)	80 (76; 85)	<0.01	0.11
FRS (%)	8.7 (6.0; 11.4)	2.8 (1.7; 6.4)	<0.01	<0.01
VO_2max (mL/kg/min)	29.5 (25.3; 34.2)	41.7 (36.5; 45.7)	<0.01	<0.01
MVPA weekly minutes	340 (103; 610)	480 (270; 920)	<0.01	0.06
QoL - Physical	67.9 (60.7; 78.6)	75.0 (67.9; 82.1)	<0.01	0.01
QoL - Psychological	70.8 (58.3; 79.2)	75.0 (62.5; 83.3)	0.01	<0.01
QoL - Social	66.7 (58.3; 75.0)	75.0 (58.3; 75.0)	0.02	0.17
QoL- Environmental	65.6 (59.4; 75.0)	71.9 (62.5; 78.1)	<0.01	0.51
PSQI	6 (4; 9)	6 (4; 9)	0.49	0.37
Glucose (mg/dL)	92 (87; 99)	88 (83; 93)	<0.01	<0.01
TC (mg/dL)	194 (166; 221)	184 (158; 209)	0.01	0.30
Triglycerides (mg/dL)	150 (126; 215)	91 (71; 136)	<0.01	<0.01
HDL-C (mg/dL)	42 (37; 47)	46 (41; 54)	<0.01	<0.01
LDL-C (mg/dL)	126 (98; 154)	115 (93; 139)	0.01	0.04
Non-HDL-C	153 (126; 177)	135 (111; 160)	<0.01	0.03
LH (mIU/mL)	3.33 (2.40; 4.35)	3.64 (2.56; 4.51)	0.09	0.65
FSH (mIU/mL)	3.3 (2.2; 4.5)	3.1 (2.2; 4.7)	0.74	0.09

TT: total testosterone; BMI: body mass index; SBP: systolic blood pressure; FRS: Framingham risk score; MVPA: Moderate-to-vigorous physical activity; QoL: Quality of Life – no unit; PSQI: Pittsburgh sleep quality index – no unit; p: Mann-Whitney U test p-value; adj: age-adjusted p-value.

Finally, we describe the prevalence of cardiometabolic risk factors in each investigated outcome: LOH, MS, and Ob. Hypertension prevalence was 65.4%, 53.4,% and 50.0%, respectively. Excess triglycerides prevalence was 69.2%, 77.7%, and 46.1%, respectively. Hyperglycemia prevalence was 34.6%, 36.9%, and 56.0%, respectively.

Elevated total cholesterol prevalence was 50.0%, 56.3%, and 54.3%, respectively. Low HDL prevalence was 50.0%, 61.2%, and 39.9%, respectively. Excess LDL prevalence was 65.4%, 68.0%, and 69.6%, respectively. Excess non-HDL cholesterol prevalence was 69.2%, 69.9%, and 65.2%. We highlight that all these prevalence estimates were very high among FFs presenting at least one of the three investigated outcomes. The lowest prevalence was hyperglycemia, corresponding to more than one-third of FFs with LOH. The highest one was excess of non-HDL cholesterol, which was present in more than two third of FFs with metabolic syndrome.

5.4 SERUM TOTAL TESTOSTERONE LEVELS IN ASSOCIATION WITH CARDIOVASCULAR RISK FACTORS, FITNESS, AND QUALITY OF LIFE

We performed a series of exploratory analyses to investigate the relationship between serum total testosterone, cardiovascular risk, and different variables. The correlation between serum TT and age, BMI, VO_2max, FRS, PSQI, QoL, and physical activity are shown in Figures 6-9. There was a negative correlation between TT levels and age, BMI, and FRS. VO_2max, physical activity, and the physical domain of QoL showed a positive correlation with TT levels.

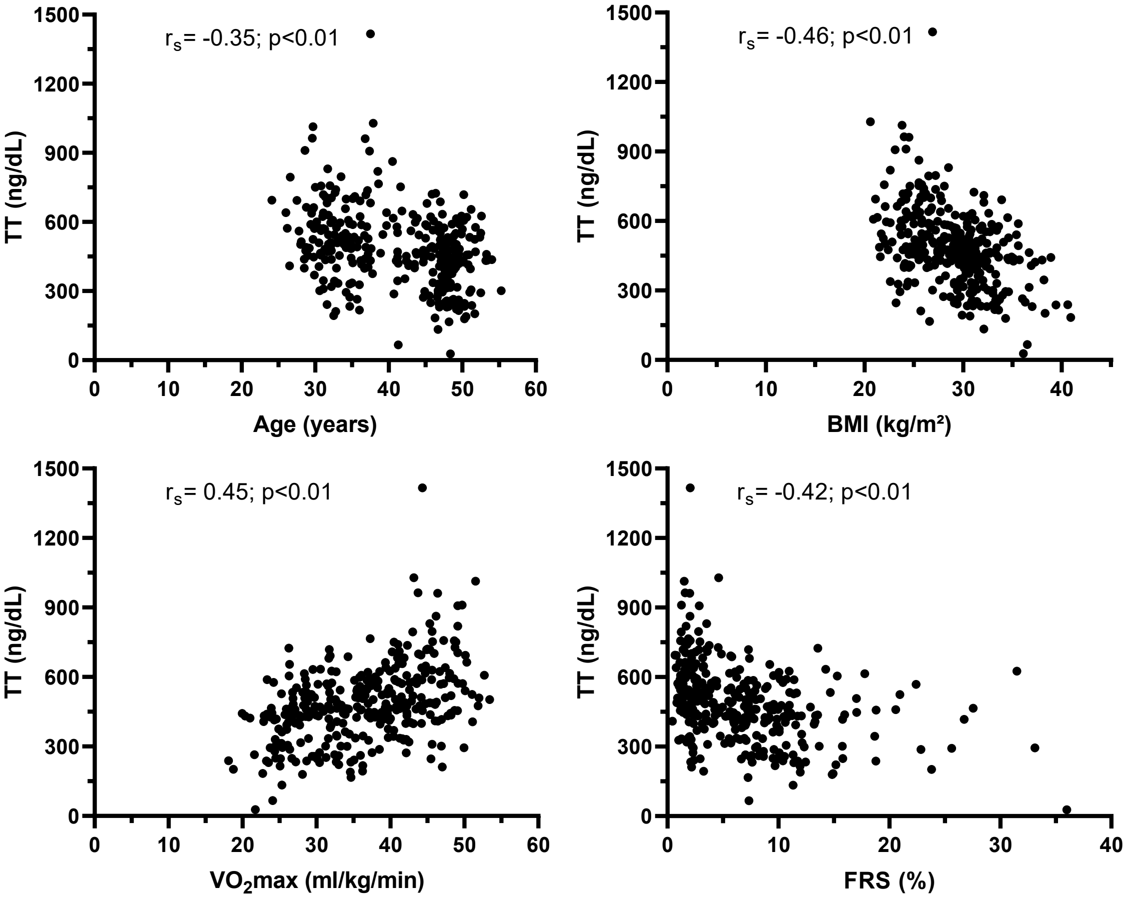

Figure 6: Correlation between serum total testosterone (TT) levels and age, body mass index (BMI), VO2max, and Framingham risk score (FRS).

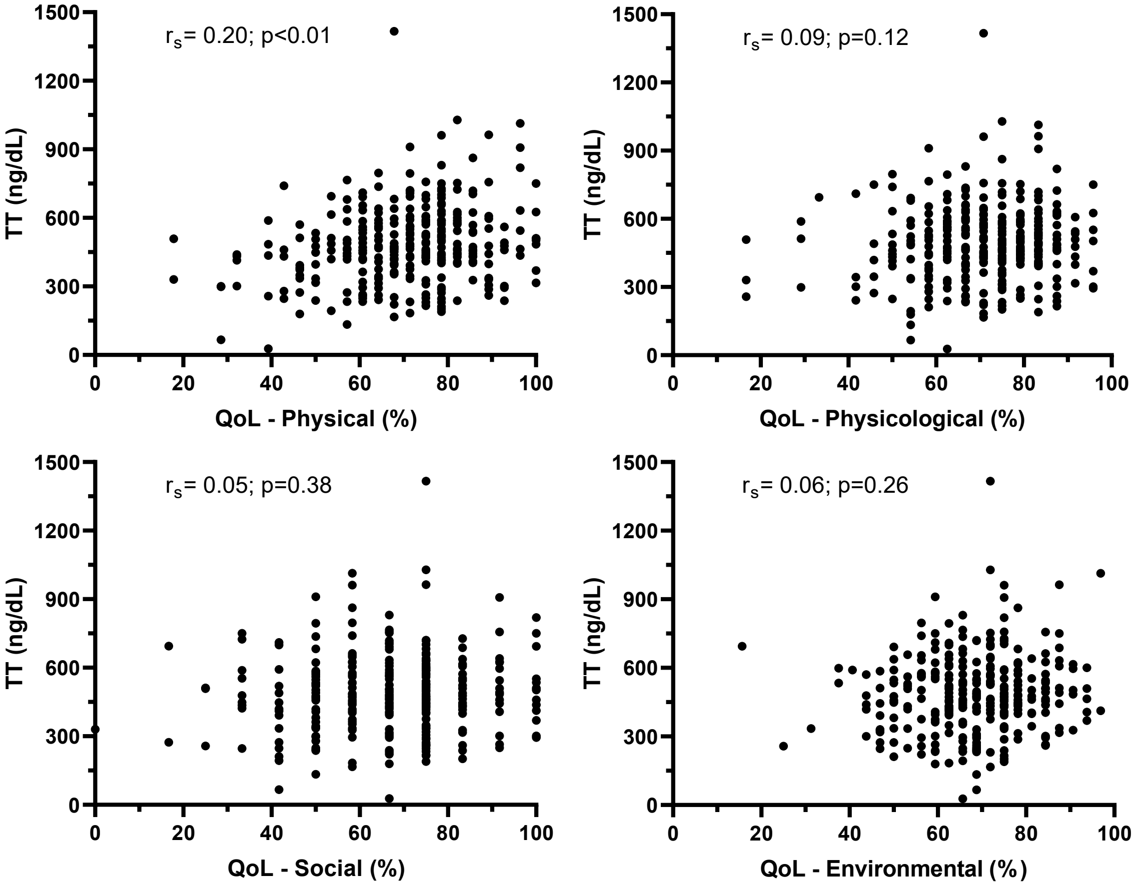

Figure 7: Relationship between serum total testosterone (TT) levels and diffent quality of life (QoL) domains.

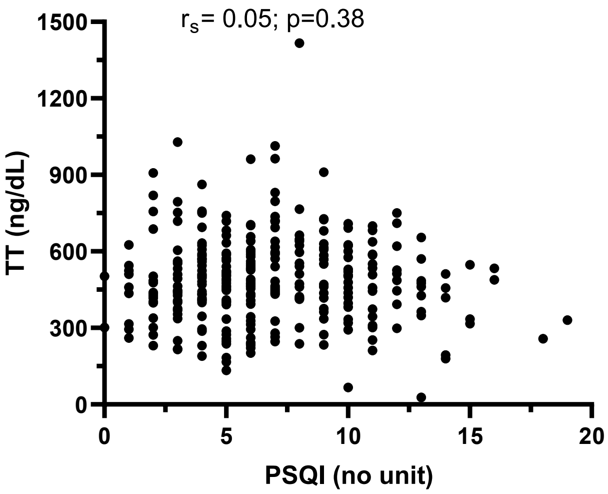

Figure 8: Relationship between serum total testosterone (TT) levels and Pittsburgh sleep quality index (PSQI) levels.

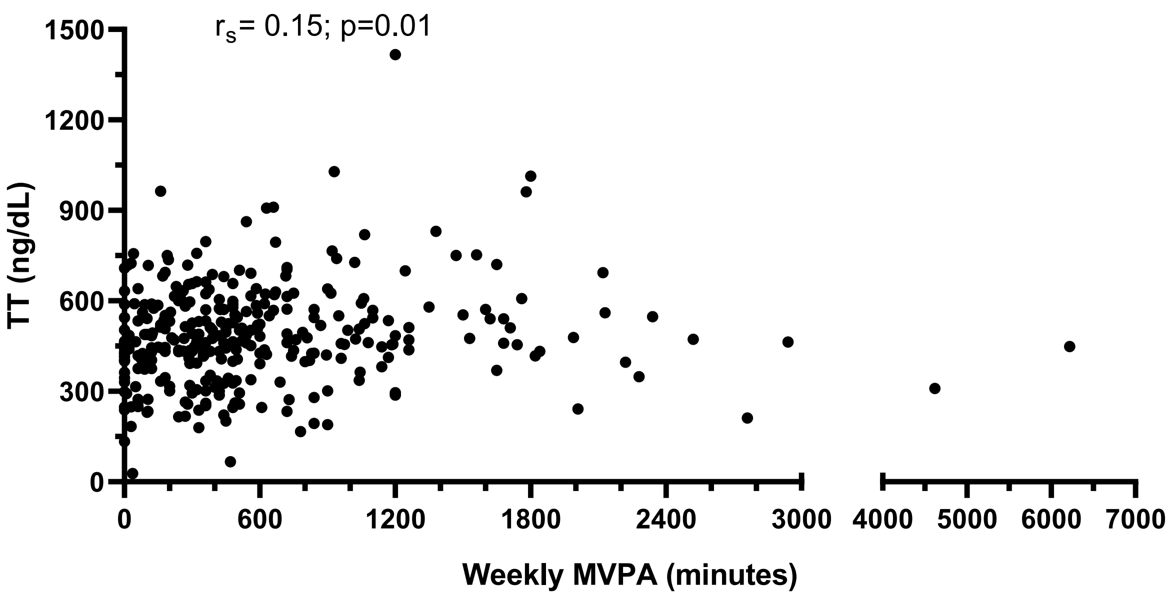

Figure 9: Relationship between serum total testosterone (TT) levels and weekly moderate-to-vigorous physical activity (MVPA) minutes. Vigorous minutes are doubled.

To better understand the effect of BMI, age, and VO_2max and possible predictors of serum TT levels in male FFs, we performed a generalized linear model to investigate the relationship between these variables due to their interrelated nature, i.e., BMI tends to increase with age, while VO_2max decreases. The model constructed significantly predicted TT (p<0.01), having as independent predictors BMI (p<0.01) and VO_2max (p=0.04). While controlling for age and VO_2max, an increase in one BMI unit would decrease by 2.6% in serum TT levels. An increase in one unit of VO_2max would result in a rise of 0.9% in serum TT levels while controlling for age and BMI. Age did not significantly affect serum TT levels when controlling for BMI and VO_2max (p=0.72), with a unit increase resulting in a reduction of 0.1% in serum TT levels.

To further investigate the relationship between serum TT and cardiovascular risk, we analyzed two-way, in a continuous and categorical form. Table 17 presents the sample distribution of FFs with different TT levels in various cardiovascular risk categories. In the crude analysis, there were significant differences between categories. We highlight the almost three-fold increase in the proportion of low-risk CV risk as you increase the TT levels from the lower category to the reference range (400-916 ng/dL, bold percentages).

Similarly, the proportion of high-risk FFs in the low TT range was 3.4 times greater than the proportion in the reference range group.

Table 17: Distribution of different testosterone levels by cardiovascular risk categories

Testosterone levels (ng/dL) n (%)	Low risk (n=152)	Intermediate risk (n=151)	High risk* (n=25)	p-value	Adj. p-value
<320	10 (6.6) **(18.2)**	35 (23.2) **(63.6)**	10 (40.0) **(18.2)**	<0.01	0.06
320-399	10 (6.6) **(34.5)**	17 (11.3) **(58.6)**	2 (8.0) **(6.9)**		
400-916	127 (83.6) **(53.1)**	99 (65.6) **(41.4)**	13 (52.0) **(5.4)**		
>916	5 (3.3) **(100.0)**	0 (0.0) **(0.0)**	0 (0.0) **(0.0)**		

*: Two very high-risk participants are included in this category; p-value: Chi-square test; Adj: Adjusted for age and BMI. Bold values represent line percentages, and non-bold are column percentages.

We modeled Framingham Risk Score (FRS) twice using a generalized linear model to investigate further the relationship between CV risk and TT. First, to better understand their relationship, we used only serum TT. Second, we performed a similar analysis using serum TT, BMI, and VO2max. Age and blood parameters were not used because they are already part of the FRS. Both models significantly explained FRS ($p<0.01$). TT was related significantly to FRS when alone ($p<0.01$) and when controlling for the other variables ($p=0.01$). This time BMI was not significant ($p=0.09$), while VO_2 max was ($p<0.01$). While controlling for BMI and VO_2max, an increase in one unit of serum TT (ng/DL) would result in an FRS decrease of 0.05%.

5.5 LOGISTIC REGRESSION ANALYSES

To explore potential predictors for the primary outcomes investigated (LOH, MS, and obesity), we performed a logistic regression analysis for each one of them (Tables 18 to 20). The analysis includes bivariate (crude) and multivariate (adjusted) analyses for each one of the outcomes.

Table 18: Analysis of late-onset hypogonadism in association with various potential predictors or correlated factors

	Late-onset Hypogonadism (n = 328)		Bivariate analysis (crude)		Adjusted analysis	
	Yes	No	p*	OR (IC 95%)	p**	OR (IC 95%)
Type of work						
Shiftwork	12 (6.2%)	182 (93.8%)	0.17	0.57 (0.25 – 1.26)	0.17	0.51 (0.19 – 1.34)
Office hours	14 (10.4%)	120 (89.6%)				
Income						
5-10 m.w.	15 (8.6%)	159 (91.4%)	0.63	1.22 (0.54 – 2.74)		
>10 m.w.	11 (7.2%)	142 (92.8%)				
Age			<0.01	1.14 (1.06 – 1.22)	0.41	1.05 (0.94 – 1.16)
BMI			**<0.01**	**1.43 (1.26 – 1.63)**	**<0.01**	**1.32 (1.13 – 1.56)**
LDL-C			0.16	1.01 (1.00 – 1.02)	0.26	1.01 (1.00 – 1.02)
Glucose						
High	9 (19.1%)	38 (80.9%)	<0.01	3.68 (1.53 – 8.84)	0.16	2.15 (0.74 – 6.22)
Normal	17 (6.0%)	264 (94.0%)				
Triglycerides						
High.	18 (16.4%)	92 (83.6%)	<0.01	5.14 (2.16 – 12.24)	0.13	2.23 (0.79 – 6.32)
Normal	8 (3.7%)	21 (96.3%)				
HDL-C						
<40 mg/dL	13 (13.7%)	82 (86.3%)	0.02	2.68 (1.19 – 6.03)	0.72	1.20 (0.43 – 3.35)
≥40 mg/dL	13 (5.6%)	220 (94.4%)				
Hypertension						
Yes	17 (14.8%)	17 (85.2%)	<0.01	3.93 (1.69 – 9.14)	0.22	1.87 (0.60 – 5.05)
No	9 (4.2%)	9 (95.8%)				
CRF						
<12 METs	25 (10.8%)	207 (89.2%)	0.02	11.47 (1.53 – 85.93)	0.55	0.47 (0.04 – 5.59)
≥12 METs	1 (1.0%)	95 (99.0%)				
PA level						
Not active	12 (17.9%)	55 (82.1%)	<0.01	3.83 (1.68 – 8.75)	0.11	2.21 (0.83 – 5.93)
Active	14 (5.4%)	246 (94.6%)				
Bad sleep quality						
Yes	14 (7.7%)	169 (92.3%)	0.84	0.92 (0.41 – 2.05)		
No	12 (8.3%)	133 (91.7%)				

** Logistic regression; m.w.: Minimum wage; BMI: body mass index; FRS: Framingham risk score; CRF: cardiorespiratory fitness; METs: metabolic equivalent; PA: physical activity level; CV: cardiovascular; OR: odds-ratio.

Table 19: Analysis of metabolic syndrome in association with various potential predictors or correlated factors

	Metabolic syndrome (n = 328)		Bivariate analysis (crude)		Adjusted analysis	
	Yes	No	p*	OR (IC 95%)	p**	OR (IC 95%)
Type of work						
Shiftwork	61 (31.4%)	133 (68.6%)	0.99	1.00 (0.62 – 1.60)		
Office hours	42 (31.3%)	92 (68.7%)				
Income						
5-10 m.w.	59 (33.9%)	115 (66.1%)	0.26	0.76 (0.48 – 1.22)		
>10 m.w.	43 (28.1%)	110 (71.9%)				
TT			**<0.01**	**0.99 (0.99 – 1.00)**	**<0.01**	**1.00 (0.99 – 1.00)**
Age			**<0.01**	**1.12 (1.08 – 1.17)**	**0.03**	**1.05 (1.01 – 1.10)**
CRF						
<12 METs	**99 (58.6%)**	**133 (41.4%)**	**<0.01**	**17.12 (6.09 – 48.16)**	**<0.01**	**6.91 (2.22 – 21.47)**
≥12 METs	4 (2.1%)	92 (97.9%)				
PA level						
Not active	31 (61.2%)	36 (38.8%)	<0.01	2.25 (1.30 – 3.90)	0.31	1.39 (0.74 – 2.61)
Active	72 (37.3%)	188 (62.7%)				
Bad sleep quality						
Yes	55 (30.1%)	128 (69.9%)	0.56	0.87 (0.54 – 1.39)		
No	48 (33.1%)	97 (66.9%)				

** Logistic regression; m.w.: Minimum wage; BMI: body mass index; FRS: Framingham risk score; CRF: cardiorespiratory fitness; METs: metabolic equivalent; PA: physical activity level; CV: cardiovascular; OR: odds-ratio.

Table 20: Analysis of obesity in association with various potential predictors or correlated factors

	Obesity (n = 328)		Bivariate analysis (crude)		Adjusted analysis	
	Yes	No	p*	OR (IC 95%)	p**	OR (IC 95%)
Type of work						
Shiftwork	77 (39.7%)	117 (60.3%)	0.80	1.12 (0.49 – 2.50)		
Office hours	61 (45.5%)	73 (54.5%)				
Income						
5-10 m.w.	81 (46.6%)	93 (53.4%)	0.63	0.82 (0.37 – 1.85)		
>10 m.w.	56 (36.6%)	97 (63.4%)				
TT			**<0.01**	**0.99 (0.99 – 1.00)**	**<0.01**	**1.00 (0.99 – 1.00)**
Age			**<0.01**	**1.17 (1.12 – 1.21)**	**0.01**	**1.06 (1.02 – 1.11)**
High glucose						
Yes	**35 (74.5%)**	**12 (25.5%)**	**<0.01**	**5.04 (2.51 – 10.14)**	**0.04**	**2.37 (1.03 – 5.47)**
No	103 (36.7%)	178 (63.3%)				
HDL-C						
<40 mg/dL	55 (57.9%)	40 (42.1%)	<0.01	2.45 (1.53 – 4.05)	0.44	1.29 (0.68 – 2.44)
≥40 mg/dL	83 (35.6%)	150 (64.4%)				
Hypertension						
Yes	72 (62.6%)	43 (37.4%)	<0.01	3.73 (2.32 – 6.01)	0.20	1.49 (0.81 – 2.75)
No	66 (31.0%)	147 (69.0%)				
CRF						
<12 METs	**136 (58.6%)**	**96 (41.4%)**	**<0.01**	**66.58 (16.02 – 276.77)**	**<0.01**	**23.29 (5.22 – 103.97)**
≥12 METs	2 (2.1%)	94 (97.9%)				
PA level						
Not active	41 (61.2%)	26 (38.8%)	<0.01	2.65 (1.53 – 4.60)	0.27	1.47 (0.74 – 2.91)
Active	97 (37.3%)	163 (62.7%)				
Bad sleep quality						
Yes	71 (38.8%)	112 (61.2%)	0.18	0.74 (0.48 – 1.15)	0.07	0.57 (0.32 – 1.04)
No	67 (46.2%)	78 (53.8%)				

** Logistic regression; m.w.: Minimum wage; BMI: body mass index; FRS: Framingham risk score; CRF: cardiorespiratory fitness; METs: metabolic equivalent; PA: physical activity level; CV: cardiovascular; OR: odds-ratio.

6. DISCUSSION

In this unprecedented cross-sectional study with a representative and randomly selected sample of 328 male FFs, we found prevalence estimates of 3.2% (1.9-5.2%), 17.0% (13.0-22.0%), and 16.9% (13.4-21.0%) for late-onset hypogonadism (LOH), metabolic syndrome (MS) and obesity (Ob), respectively. To the best of our knowledge, this is an important original finding since no previous study has estimated LOH prevalence in the Fire Service using two total testosterone measurements and symptoms. Similarly, MS prevalence has been described in various FFs samples worldwide. However, we highlight the originality of this finding since we believe this is the first Brazilian population estimated prevalence to be reported. Besides, this first report on Brazilian FFs' MS prevalence estimate represents a Brazilian state – *Distrito Federal*.

Importantly, Brazilian FFs are military career firefighters, which also brings novelty compared to other studies investigating MS within the fire service. Also, regarding obesity prevalence, an exciting novelty is having access to the entire population dataset. The proportion of FFs with BMI-defined obesity in 2019 and 2021 in the population from where our sample came were 14.4% and 15.0%, respectively. Despite time differences, these values are very close to the one estimated by our sample, especially considering the 95%CI. This obesity data reinforces the success of our strategy, boosting our confidence in the LOH and MS prevalence estimates in which there is no population data available to compare.

Importantly to highlight, in our study, the late-onset male hypogonadism classification was based on the gold-standard criterion, which includes two total testosterone (TT) measurements plus the presence of signs and symptoms (using the androgen deficiency in the aging male questionnaire – ADAM) (BHASIN et al., 2018). Considering that there are health risks associated with testosterone replacement therapy, especially increased risk for prostate cancer, the US Endocrine Society proposes this criterion to define LOH for treatment decisions. So, also considering that the association of LOH and low TT levels on cardiometabolic health is still an open field, we decided to adopt the same rigorous criterion when investigating LOH prevalence and its association with other cardiometabolic variables, increasing the robustness of our findings. Exceptionally, we included FFs who did not complete the 2nd measurement but had a positive result in the ADAM questionnaire (ADAM+) and a 1st TT measurement

<264ng/dL. This decision was based on the fact that all other FFs with an ADAM+ and a TT<264 ng/dL in the first measurement presented TT<320 ng/dL in the second measurement. To expand our analysis, we also estimated the population prevalence of different ways to classify LOH (or low TT), with prevalence increasing as the criteria became less stringent. For example, using only one TT measurement resulted in a prevalence more than two times greater than two measurements and ignoring signs and symptoms, while using only one TT measurement resulted in a prevalence almost five times greater (Table 3).

We also investigated the association between LOH, MS, and Ob prevalence per our study aims. Our "gold-standard" LOH definition was significantly associated with MS. 81% of the LOH group had MS. Compared to a reference group (ADAM-, TT ≥ 400 ng/dL), FFs with LOH had an age-adjusted odds 11.5 times greater of having MS. This is vastly different compared to the less stringent criteria examining only TT, which had 5.0 times greater odds of having MS compared to the reference group (Table 6). Notably, the fact that this association remained significant even when using only one TT measurement has important practical implications since it may be used as a screening strategy in the Fire Service to early identify FFs who may benefit from lifestyle change intervention before a consistent pattern of low TT or the manifestation of LOH signs and symptoms.

As expected, Ob and LOH were also significantly associated. While we found that the prevalence of LOH among obese FFs was 13.7%, almost all FFs with LOH were obese (92%), showing the strong impact of obesity on LOH. The causal relationship between obesity and LOH is beyond the scope of our study. Still, our findings suggest similarities with other best-known clinical conditions, like the association between tobacco and lung cancer. While tobacco is responsible for 80-90% of lung cancer cases, a much lower proportion of smokers develop lung cancer (THANDRA et al., 2021). A caveat must be considered since secondary hypogonadism has a broad spectrum of possible causes (BHASIN et al., 2018), but our data reinforce a potential preponderant role of obesity. Also, compared to the reference group, LOH FFs had 42 times greater odds of obesity. When adjusting for age, LOH FFs had 11.5 times greater odds of having obesity. Again, the less stringent criteria presented a smaller age-adjusted odds ratio (4.9). However, two low TT results had age-adjusted odds of 11.7, the closest value to the LOH group (Table 7). The interpretation of possible clinical or physiological implication of the difference in the strength of the association observed is beyond our study but deserve further investigation.

We also analyzed the prevalence of other groups which are not classically classified as hypogonadal but could warrant endocrinological treatment or be at a greater cardiometabolic risk. Subclinical hypogonadism (TT< 320 ng/dL in both measurements and lack of signs and symptoms) and borderline hypogonadism (ADAM+, 1st TT 320-399 ng/dL but 2nd TT <264). Again, the investigation of those two conditions (subclinical hypogonadism and borderline hypogonadism) was not in our study's scope but emerged as important findings. Both groups showed prevalence estimates of around 2 – 2.5% and represented conditions that would need further investigation in a clinical or occupational health setting. In both cases, FFs might benefit from treatment (pharmacological or non-pharmacological), considering that it may also be associated with increased cardiovascular risk despite not meeting formal criteria for LOH. In other words, both situations might represent preclinical conditions and a window of opportunity for cardiometabolic and endocrine preventive interventions in firefighters. Considering these two conditions and LOH, we found that around 8% of the studied firefighter population would benefit from early detection. Of note, this proportion of conditions less known and less screened but potentially associated with significantly increased cardiometabolic risk is almost equivalent to the Brazilian prevalence of diabetes in men (8.6%) or its correspondent value in the same state of our study – Distrito Federal (9.0%) (BRAZIL, 2022).

6.1. PREVALENCE RESULTS

6.1.1 LOH prevalence and associations

We observed an estimated late-onset hypogonadism (LOH) population prevalence of 3.2% (1.9-5.2%) in working male military firefighters (FFs). The prevalence of LOH may vary significantly based on the criteria used for classification. For example, TT or free testosterone, the cut-off point used, single or repeated measurements, and how signs and symptoms were evaluated. This is easily seen in Table 3, in which prevalence more than doubles when only the first measurement is considered. If signs and symptoms are not taken into account, prevalence doubles again, reaching 14.9%. In a systematic review of hypogonadism prevalence (ZAROTSKY et al., 2014), data from large population-based studies showed a LOH prevalence of 2.1 to 12.8%. The largest one (12.8%) did not include signs and symptoms, only TT as a criterion (<300 ng/dL). The smallest one (2.1%), which is very similar to our result, included TT (<317 ng/dL) and signs and symptoms, but only the sexual-related ones. Two US-based studies found a very similar prevalence of LOH (5.6% and 6.0%) using a similar range of TT values but combined with free testosterone and sexual and non-sexual signs and symptoms. Thus, restricting the type of symptoms to categorize LOH also affects prevalence. Importantly, none of these studies used two measurements on separate days like ours.

In our study, out of the 45 FFs with TT<320 in their 1st measurements, 14 (31.1%) had a 2nd measurement ≥320 ng/dL. Thus, studies using only one measurement might be overestimating LOH prevalence. However, out of the 43 measurements between 320-399 ng/dL, 13 (30.2%) had a second value of TT <320 ng/dL (Table 6). Thus, it is not easy to estimate the true impact of a second measurement in the prevalence estimate. Interestingly, when considering 18 FFs with <264 ng/dL in their 1st measurement, only one had a second measurement >320 ng/dL. This last case was extreme because it was a triathlete training for a competition, and in 72 hours, his TT levels went from 131 to 545 ng/dL, as explained in the results section. Of note, this volunteer had no symptoms (ADAM-). These findings highlight the need to use a more strict cut-off point when only one TT value is available to increase the accuracy of the prevalence estimate. Regardless, using only one TT without evaluating signs and symptoms prevents the identification of LOH. Notably, these results strengthen our decision to apply research to the gold-standard criterion recommended for clinical decision-making, as well as the confidence in previous publications of our group, in which we made this decision (LOFRANO‐PORTO et al., 2020; RANADIVE et al., 2021).

Age also may affect LOH prevalence since a decrease in serum TT values is expected with aging. Hypogonadism prevalence tends to increase after men reach the fourth decade of life (THIRUMALAI; ANAWALT, 2022). A study with over 7000 Australian men aged between 35-99 years, including more than 10.000 serum samples, observed a slight decline in TT after age 35, with a steeper decrement after 80 years of age (HANDELSMAN et al., 2015). The stricter age range of the investigated population (22-55 years old) is likely why age was not a significant independent predictor of serum TT in our study when adjusting for BMI and VO_2max simultaneously. In our logistic regression analysis, only BMI remained significant in the larger model among various possible predictors of LOH. Notably, the relatively low prevalence of LOH is probably also affected because our population was composed of middle-aged adults with high job-related physical demands.

BMI significantly impacts serum total testosterone values, presenting an inverse linear relationship (DANDONA; ROSENBERG, 2010). Reported prevalence values in groups with obesity range from 30-75%, depending on the severity of obesity (TRAISH, 2014). Another example of this relationship is the reversal of LOH after bariatric surgery. Middle-aged men with severe obesity (mean BMI of 50 kg/m^2) presented a LOH prevalence of 79% before bariatric surgery, and one year after the surgery prevalence dropped to 6%. All of this was accompanied by a mean weight loss of 60 kg resulting in a mean BMI of 32 kg/m^2 (PELLITERO et al., 2012). In our sample, 92% of FFs with LOH had obesity compared to the study sample prevalence of 42.1% (enriched sample). In our adjusted predictor analysis, a one-unit increase in BMI resulted in a 32% increase in the odds of having LOH (Table 18). Figure 4 also presents the impact of BMI on LOH prevalence, with prevalence rates in the normal and overweight (2.9% and 0.4%, respectively) increasing drastically in the obesity category (13.7%). Another very prevalent condition in the LOH group was below-average fitness (CRF <12 METs), showing once more the possible positive effect of CRF on low TT or LOH prevention.

In our data, the LOH group presented a lower VO_2max compared to the reference group, or the sample as a whole, even when adjusting for age and BMI (Tables 13-14), with 96.1% having CRF ≤ 10 METs, compared to the reference group which had only 24.3% of FF in this category. Also, the reference group had 51.4% with CRF>12 METs. Of all FF with a CRF>14 METs, 78.6% were in the TT reference group. VO_2max was an independent predictor of serum TT, but having CRF <12 METs was not considered an independent predictor of LOH. We are not the first cross-sectional study to observe a significant association between VO_2max and serum TT. In a Cooper Center study, LOH prevalence was associated with BMI and VO_2max, but not age. Also, VO_2max was a significant independent predictor of serum TT (DEFINA et al., 2018). These findings are very similar to ours, despite their sample being a very different age from ours (50-80). Cross-sectional studies do not allow us to speak of causation between variables, so it would be too early to propose increasing CRF to improve TT levels and decrease LOH prevalence. One intervention study among middle-aged men who exercised for 12 weeks showed that while serum TT levels did not change in those with normal BMI, those with overweight or obese BMI experienced a significant increase in serum TT levels. This improvement was significantly associated with the increase in vigorous PA minutes even after adjusting for confounders (Age, BMI, insulin levels, and others) (KUMAGAI et al., 2018). On the other hand, another clinical trial showed no significant variation in TT, while VO_2max increased in middle-aged men after 12 months of aerobic training (HAWKINS et al., 2008). The relationship between CRF fitness and TT levels still deserves further studies. The discrepancy in results between studies might indicate that other factors, such as BMI, might mediate this relationship. Our data support this possibility once some significant associations observed in the bivariate analysis lose significance after adjusting to BMI.

To the best of our knowledge, this is the first population estimate of LOH from a randomized and representative cross-sectional study in FFs. Our group has previously published data on low TT in US FFs (single measurement, no report of symptoms), but this may be the closest to what we have available for FFs (LOFRANO‐PORTO et al., 2020; RANADIVE et al., 2021). Both studies evaluated slightly different parts of a sample of male career FF performing routine occupational medical exams. The prevalence of low TT was 11%, but the cut-point was <264 ng/dL. This difference in prevalence values could also result from a greater obesity prevalence (36% vs. 17% of our study), especially since BMI was the best predictor of LOH, even when correcting for age, VO_2max, elevated glucose, and various other factors. Brazilian FFs are also military. Thus, the best comparison would be with other military groups. One study analyzed LOH prevalence retrospectively in male Brazilian military performing routine health exams and found a LOH prevalence of 19.8%. However, they also included retired military men (age range: 24-87) and found a significant reduction of TT levels with age, e.g., military with age ≤ 40 years had mean TT levels of 821 ng/dL, while those in the 41-50 range had 599 ng/dL. Most importantly, the study did not assess signs and symptoms and thus can not be considered “true” LOH, only low TT. This means that the prevalence could be less than half of this, especially if deemed an age similar to ours (22-55 years).

Finally, it is essential to mention that our sample is composed of active male working military FFs. This means that primary hypogonadism and some causes of hypogonadism which are somewhat rare in the general population are probably absent in our study, e.g., Klinefelter syndrome, testicular injuries, or cancer, Cushing syndrome, androgen deprivation therapy for prostate cancer (THIRUMALAI; ANAWALT, 2022) since those conditions would probably impose duty restrictions to FFs.

We end this section by highlighting the importance and originality of our study. To the best of our knowledge, this is the first study, not only in FFs but in general, to investigate LOH according to major guidelines like the Endocrine Society (BHASIN et al., 2018), including two separate serum measurements and signs and symptoms. Another originality is the extensive investigation in younger ages (<40 years) which is not a usual focus of hypogonadism studies. Table 6 is essential to see the importance of a second measurement. The Endocrine Society guidelines recommend further examination when TT <400 ng/dL and in specific situations (BHASIN et al., 2018). Of the 43 FFs who had a TT between 320-399 ng/dL in the first measurement, some remained with TT >320 ng/dL (15; 34.9%), representing a group that, due to possessing characteristics similar to those with low TT (<320 ng/dL) and reference range (400-916 ng/dL) – Table 5 - could warrant further monitoring for cardiometabolic risks and need for hypogonadism treatment when symptoms are present. Thus, monitoring LOH through a single measurement and without screening for symptoms besides increasing prevalence (Table 3), might misclassify individuals, possibly leading to an increase in unnecessary testosterone use, which already is a problem, especially in younger men (BUSNELLI; SOMIGLIANA; VERCELLINI, 2017; DE RONDE; SMIT, 2020; JAMES; WYNN, 2022).

6.1.2 MS prevalence and associations

We observed an estimated metabolic syndrome (MS) population prevalence of 17.0% (13.0-22.0%) in working male military FFs. MS prevalence in the Fire Service varies considerably between countries and regions. In US FFs, a large cohort (n=940) of Colorado volunteer and careers FFs had an MS prevalence of 10% (LI et al., 2017). Previous work on the same region but with a smaller sample (n=214) observed an MS prevalence of 15% (DONOVAN et al., 2009). These results contrast with data from a large midwestern cohort of career FFs, which observed a more considerable MS prevalence: of 28.3% (BAUR; CHRISTOPHI; KALES, 2012). When comparing prevalence data with FFs from other countries, we also observed significant variation in MS prevalence, 21.4% in Korean FFs (LEE; KIM, 2017) and 14.4% in German FFs (STRAUSS et al., 2016). The latter used the International Diabetes Federation (IDF) criteria for SM, meaning that abdominal obesity is obligatory, and thus, prevalence using the harmonized criteria is probably higher. Another interesting comparison is with a group of middle-aged Brazilian civil servants in a security and transportation department (MILESKI et al., 2015). They observed a prevalence of 24.1%. In this study, similar to our case, the three most frequent MS components were high-blood pressure, obesity, and high triglyceride level.

To understand the variation in MS prevalence and to compare between groups, it is crucial to investigate its predictors. In our study, age, serum TT, and CRF <12 METs were all independent predictors in our fully adjusted model. It is well established that older individuals are at greater risk for MS (ECKEL et al., 2010); for example, age was also an independent predictor of MS in Korean FFs (LEE; KIM, 2017) to the point is common to have age-adjusted comparisons in MS studies (BAUR; CHRISTOPHI; KALES, 2012; STRAUSS et al., 2016). MS has also been associated with low CRF in previous FF research (BAUR; CHRISTOPHI; KALES, 2012). In the just mentioned work, age was not an independent predictor of MS when accounting for CRF, with the latter remaining significant. Lastly, we are the first to explore the relationship between serum TT and metabolic syndrome in FFs. Increasing serum TT led to a decrease in the odds of having MS. The effect was significant but apparently small (Table 19), with the odds ratio being discernable at the fourth decimal house. This is because we used TT as a continuous variable; thus, every one-unit increase led to a very small impact – as would be expected. Going from 320 to 321 ng/dL of TT is unlikely to affect one's organism significantly. We are not the first to investigate this association; a systematic review and meta-analysis on this topic found that MS was a significant independent predictor of low TT. Individuals with MS had lower TT than those without (mean difference of 87 ng/dL) (CORONA et al., 2011a).

6.1.3 Obesity prevalence and associations

We observed an estimated obesity (Ob) population prevalence of 16.9% (13.4-21.0%) in working male military FFs. Ob prevalence in the Fire Service has been thoroughly investigated. We are currently working on a systematic review of the worldwide Ob prevalence in the Fire Service (SOARES; SMITH; GROSSI PORTO, 2020). Ob prevalence will vary significantly based on the country, region, and types of FF. For example, in US FFs, BMI-based Ob prevalence has been reported between 14.0 – 59.4%. The systematic review that we are currently working on points to volunteer FFs typically presenting a greater Ob prevalence (unpublished data). In Brazilian military FFs, our research group generally has reported data from the Fire Service, with prevalence varying from 11.5-14.7% (NOGUEIRA et al., 2016; PORTO et al., 2016; SEGEDI et al., 2020). Our population estimate of 16.9% is slightly larger but contained inside the 95% confidence interval (13.4-21.0%). Also, as previously stated, the population data was very similar. In another state of Brazil, a lower prevalence was observed, 11.0% in the state of Espírito Santo (DAMACENA et al., 2020) and a similar one (15.0%) in the city of the state of Goiás (RIBEIRO GUARESCHI et al., 2017). Thus, despite significant differences in Fire Service state structures, it is possible that due to the nature of their military characteristics, there is not so much variability as in the US regarding Ob prevalence.

When comparing our obesity prevalence with the national and local estimates in the general population, we observed a lower proportion in our FFs cohort (16.9%) as compared to the local (23.0%) and the national (22.4%) prevalence estimates among male adults. The national estimates for men between 35 – 44 years and 45 – 54 years are 25.1% and 24.3%, respectively (BRAZIL, 2022). Those two age ranges would include the majority of the FFs population. So, military career FFs from the Distrito Federal showed a lower prevalence of obesity than the general population. However, it is plausible to consider that 16.9% is a high obesity prevalence for FFs because they need good physical fitness to better respond to the high-duty physical demands and to reduce their cardiovascular risk (KALES; SMITH, 2017; STRAUSS et al., 2021). On the other hand, the observed prevalence may be considered low compared to the general population. One hypothesis that may explain the lower obesity prevalence among FFs compared to the general population is the occupational physical fitness requirement allied to the remarkable work the Fire Service of the Federal District (*Distrito Federal*) has been doing to face the obesity pandemic: building a fitness center in every firefighter battalion, medical occupation health screening every two years, and an annual mandatory physical fitness test with minimum standards that influence career progression (NOGUEIRA et al., 2016, 2021; PORTO et al., 2020).

When investigating possible predictors of obesity, we found the following variables as significant in our complete model: TT, age, high glucose, and CRF <12 METs. Damacena et al. (2020) investigated predictors of central Ob in their sample. They observed similar results, with age, physical activity (PA), CRF, high glucose, and high triglycerides as significant predictors. The Federal District is one of Brazil's most physically active states, a possible explanation for the lack of significant association of

PA with obesity when adjusted for confounders. For example, in the Damacena et al. study, physically active individuals composed 17.5% of the FFs with obesity group, while in our study, 70.3% of FFs with obesity were active. We used the IPAQ questionnaire, which may overestimate PA compared to other questionnaires (GUTHOLD et al., 2018; HALLAL et al., 2010, 2012). However, empirical evidence and studies using accelerometry agree that the FFs of our region are very active while on duty. In the case of wildland fires, some perform 150 minutes of moderate-to-vigorous activity in just one day of work (MARTIN et al., 2020; SAINT-MARTIN, 2018).

6.2. LOH, SERUM TT, FITNESS, CARDIOVASCULAR AND METABOLIC RISK

Besides addressing our prevalence results, it is crucial to interpret our findings in the context of daily job-related activities performed by this specific workforce. As previously mentioned, firefighting is a hazardous profession with high cardiovascular risk (KALES; SMITH, 2017; SOTERIADES et al., 2011). The leading cause of work-related death among US FFs is sudden cardiovascular death, accounting for 40-50% of all fatalities related to work activities (FAHY; PETRILLO, 2022). Importantly, emergency duties and cardiac pathoanatomic findings are associated with increased SCD among FF (KALES et al., 2007; SMITH et al., 2018). In a large case-control study with a US representative sample of firefighters´ autopsies, Smith and colleagues found that more them two third of cardiac fatalities in male firefighters (aged 18–65 years) had evidence of coronary artery disease (≥75% stenosis) and cardiomegaly (SMITH et al., 2018). Also, the same group, based on the same autopsies records, has shown that for deaths attributed to coronary heart disease (CHD) and cardiomegaly, emergency duties such as fire suppression and alarm response were associated with a 112-fold and 7.7-fold increased risk of cardiac death, respectively, compared with non-emergency duties (station duties) (SMITH et al., 2019). Putting all together, the observed prevalence estimates acquire particular importance within this population, considering that the investigated outcomes (LOH, Low TT, MS, and Ob) are part of the complex myriad of cardiometabolic risk or, at least, share the same risk factors. Robust previous evidence, especially from The Framingham Heart Study, has shown that high blood pressure and left ventricular hypertrophy (LVH) are significant predictors of the risk of CHD. Also, high blood pressure and obesity are predictors of left ventricular hypertrophy (ANDERSSON et al., 2019). Recently, an umbrella review of 55 meta-analyses found convincing evidence (higher category of evidence) that physical activity was a protective factor against SCD in the general population. Also, hypertension was classified as a risk factor with highly suggestive evidence (TSARTSALIS et al., 2022). In this context, our findings acquire a singularity related to the characteristics of our target population. This singularity increases our findings' scientific and practical importance for the Brazilian and worldwide Fire Services. We found that FFs with LOH and low TT, compared to their peers without these conditions, had higher BMI, systolic and diastolic blood pressure, Framingham risk score, and triglycerides, apart from lower CRF and HDL-c. FFs with LOH also presented lower physical activity. Of note, the most prevalent risk factor among FFs with MS was elevated blood pressure. In addition, MS and Ob are well-recognized conditions that increase the risks for cardiovascular diseases and diabetes (ALBERTI et al., 2009; ARNLÖV et al., 2011). Diabetes alone is a risk factor for SCD, but, at the same time, it is a preventable condition if lifestyle modification is implemented in someone with prediabetes (KNOWLER et al., 2002). In summary, the observed prevalence estimates on LOH, low TT, MS, and Ob are strongly concerning in this population when the highly demanding job-related activities are considered, along with the complexity of all cardiometabolic risk factors shared by these clinical conditions.

Throughout our analysis, we observed CRF being significantly associated with cardiovascular risk, either considering MS as a risk factor or with FRS. We observed VO_2max as an independent predictor of FRS alongside TT, but not BMI. VO_2max was significantly different in all group comparisons despite adjusting for age and BMI (when possible) – Tables 13-16. In our logistic regression CRF <12 METs was strongly associated with MS and Ob. The protective effect of CRF on MS in FF has been reported previously using various methods, including maximal exercise tests (BAUR; CHRISTOPHI; KALES, 2012; DONOVAN et al., 2009; LI et al., 2017). In a study in the general population of Korea, CRF modified the association between adiposity and MS. For example, individuals with low visceral fat but unfit had a higher prevalence of MS than individuals with increased visceral fat but fit (KIM et al., 2014). Such findings agree with ours, with lower CRF being an independent risk factor, despite adiposity levels. We come back to the importance of adequate CRF in FFs, since it may be improved with exercise training. In the general population, CRF is associated with a wide array of benefits, including improving sleep quality, memory, and attention, reducing the incidence of cardiometabolic diseases, and cardiovascular and all-cause mortality (BULL et al., 2020; HASKELL, 2019).

6.2.1 Serum TT population percentiles

Following the exact percentiles of Travinson et al.(2017), we described a populational reference range using our data. This data could be used for future research and warrants further investigation with its capacity to associate with clinical outcomes. The lowest percentiles investigated (2.5th, 5.0th, 10.0th) were 233 and 261, and 306 ng/dL, while the "classical" reference range – non-obese young men – would be 264, 303, and 349 ng/dL. Of course, these data are affected by the age range and the inclusion of obese men. Our data, especially in the low end, is similar to the harmonized reference ranges for non-obese 40-49 men (2.5th: 235 ng/dL, 5.0th: 273 ng/dL, 10.0th: 310 ng/dL), which is also our mean population age.

6.3. OTHER NOTEWORTHY MENTIONS OF OUR FINDINGS

We compared various characteristics in FFs with LOH or low TT. Despite not being our primary aims, we understood it was important to be described since understanding the prevalence of these conditions also means understanding harms brought to health and quality of life (QoL) to show the need for detection and treatment of these individuals. Regarding QoL, only physical function was significantly correlated with serum TT levels (Figure 7). When comparing groups based on TT, the physical function domain of QoL was also significantly different between Low TT (<320 ng/dL) and reference range TT (400-916 ng/dL), as seen in Table 5. In contrast, when the LOH group was compared to the reference group (TT 400-916 ng/dL; ADAM-), QoL was markedly different in all four domains despite correcting for age and BMI (Table 14). Data on the European Male Aging Study (EMAS) also showed a significantly lower QoL in men with LOH compared to eugonadal men, but only in the physical domain (TAJAR et al., 2012). These results seem similar to when we compared men with LOH to the rest of the sample, where only the physical domain of QoL was different between groups (unadjusted, Table 12). The real issue here may be the referent. Comparisons with the whole sample include men who are borderline for LOH, and due to our enriched sample, a significant proportion of men with obesity and MS are also included. Such conditions are associated with reductions in QoL, as seen in our data (Tables 15-16).

We used the PSQI to evaluate sleep quality in our sample. We did not detect a significant impact or difference between the conditions studied. However, it still is noteworthy that a considerable number of FFs were classified as having bad sleep quality. Considering the reasonably high MS prevalence, future studies should investigate sleep quality in this group since short sleep duration has been associated with increased cardiovascular risk. Sleep hygiene promotion could be beneficial, especially for this group (FERNANDEZ-MENDOZA et al., 2017).

6.4. STRENGTHS AND LIMITATIONS

It is necessary to acknowledge an important limitation of our study, VO_2max was not measured directly. However, it was estimated using a validated instrument in the general population (JACKSON et al., 1990) and Brazilian Military FFs (SEGEDI et al., 2020). This instrument uses age, BMI, and PA level to estimate VO_2max. Thus, it is not possible to state if the results would be different using other methods to evaluate CRF and VO_2max. However, this is an inherent limitation of using any indirect method to assess CRF. Notably, the fact that VO_2max was significant in various analyses despite age and BMI corrections strengthens our confidence in our results, although we acknowledge the methodological limitations. However, we also must recognize that these same adjustments in the VO_2max analysis could be an "over-correction" since the equation involves physical activity, age, and BMI. Especially in the LOH group and other subclinical or borderline groups with a very high obesity rate. Thus, this adjustment could be viewed as an overcorrection since it could be interpreted that obesity is parte of the nature of data, similar to the MS and obesity analysis in which we corrected only for age. Since investigated are groups are highly associated with elevated BMI (high percentage of obesity and overweight) it is possible that the best way to represent these FF's CRF would be absolute (L/min) VO_2max, instead of relative (mL/kg/min).

A major strength of our study was its design. The use of an enriched randomized sample selection with the use of inverse probability weighting to calculate prevalence was a robust approach. Due to the relatively low prevalence of LOH in the target population, a simple randomization would probably result in a few cases, preventing, for example, the association analyses. The confirmation of the estimated obesity prevalence using population obesity prevalence increased our confidence in our estimates even further. Performing two blood measurements to confirm low testosterone was also a robust methodological choice. This option is time-consuming and increases costs, which is possibly the reason why not many studies employ this. However, in the end, we have a one-of-a-kind outcome, a robust population prevalence derived from a randomized sample following “gold-standard” Endocrinology guidelines to characterize LOH – two TT dosages associated with signs and symptoms.

6.5 – PRACTICAL ASPECTS AND PERSPECTIVES

Our findings have important implications both for research and occupational perspectives. On one hand, our results contribute to a better understanding of the LOH prevalence, as well as its associations in a very specific professional category. On the other hand, our study may contribute to establishing screening protocols by the occupational health team, aiming at early detection of relatively new clinical conditions associated with an increased cardiometabolic risk.

One important result of this research is the development of a second study aiming to evaluate the impact of a lifestyle intervention based on improving diet, physical fitness, and sleep quality on serum TT levels, apart from the quality of life and traditional cardiometabolic risk factors, such as excess of body weight, total cholesterol, triglycerides, and low HDL-cholesterol. Taking those two studies together opens new perspectives for health promotion in the Fire Services.

7. CONCLUSIONS

7.1. PRIMARY CONCLUSIONS AND CLINICAL/OCCUPATIONAL IMPLICATIONS

Aiming to investigate the prevalence of late on-set hypogonadism, metabolic syndrome, and obesity in male career military firefighters, using a randomly selected and representative sample, we found population prevalence estimates of 3.2%, 17.0%, and 16.9%, respectively. LOH prevalence was significantly influenced by body mass index, even when correcting for potential confounders such as age, cardiorespiratory fitness, physical activity, high glucose levels, and high triglycerides levels. The population prevalence of LOH in FFs with obesity was 13 times greater than in FF without obesity. It is obvious that not all FFs with obesity will develop LOH. However, almost all FFs with LOH were obese (92%), and 81% of them had MS. Thus, it is crucial to understand better factors associated with LOH in order to detect cases better since they require specific treatment and seem to present a significant cardiovascular risk compared to men without LOH. The prevalence of LOH was relatively lower than in previous studies, but to the best of our knowledge, our study was the first to apply a gold-standard criterion in a research approach. As expected, MS was also strongly related to BMI. After all, obesity is a component of MS. In this firefighter's population, serum total testosterone, age, and CRF were significant independent predictors of MS. These findings reinforce the importance of maintaining adequate fitness levels throughout a FFs career since age will inevitably increase and serum TT may decrease. So CRF may be the only truly modifiable risk factor (not including BMI). Lastly, serum TT, age, CRF, and high glucose were significant predictors of obesity in our sample. Except for age, it is hard to think of them as "true mechanistic" predictors of obesity due to the bidirectional nature of these variables and the inherent limitation of a cross-sectional study. FFs with high glucose are at an increased odds of having obesity even after adjusting for confounders. FFs with high glucose that do not present obesity warrant further attention due to a possible risk of developing Ob and MS (by increasing two MS components).

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7.2. SECONDARY CONCLUSIONS

Regarding prevalence estimates of different forms of classification of late-onset hypogonadism (LOH), such as only one measurement or not using signs and symptoms, prevalence increased when criteria were “loosened,” such as using only one TT measurement, or not using signs and symptoms of LOH. Prevalence increases almost five times when comparing the most stringent to the most “liberal.” This finding is very important, not only because of the overestimation per se but because this means that some individuals could erroneously start to use testosterone, under medical supervision or not.

Also, LOH was significantly associated with metabolic syndrome (MS) and obesity (Ob), even when correcting for age. The strength of association between conditions changed when using said different forms of classification for LOH. Interestingly, the LOH criteria had the strongest association with MS when considering two TT measurements and symptoms. However, regarding the association with Ob, the strength of the association between the LOH defined by signs and symptoms and two TT measurements was basically the same if LOH was to be defined using two TT values without signs and symptoms. Serum TT was significantly associated with BMI in our study in different analyses, even after adjusting for a series of confounders. Thus, this possibly explains the lack of impact in the association between LOH and Ob of using signs and symptoms in LOH criteria. Lastly, CRF levels played an important role in our sample's LOH, MS, and Ob prevalence. The vast majority of FFs with these conditions had CRF ≤ 10 METs, and not a single FF with CRF > 14 METs. MS and Ob showed a significant difference in CRF levels distribution in the sample despite adjusting for age. Again, we see the impact of CRF levels on FF health.

When analyzing characteristics of FFs with LOH, they were generally older and had higher BMI. Considering the age and BMI-adjusted analysis, FFs with LOH had significantly lower VO_2max, weekly physical activity (minutes), and lower HDL-C. As estimated by FRS, cardiovascular risk was not different when adjusting for age and BMI. A similar pattern was observed for those with low TT compared to those in the reference group. The total amount of moderate-to-vigorous physical activity was not significantly different after adjusting for age and BMI.

In summary, irrespective of the comparisons with other studies in the general population, our prevalence data are concerningly high in workers that are well recognized as having high cardiometabolic risk due to inherent duty-related activities. Considering the presence of LOH and low TT, around 8% of the studied firefighter population, would very much benefit from early detection for conditions that are not usually screened in occupational health settings. Our findings support a call to action to implement health policies to stimulate healthy lifestyles in the Fire Service. In this scenario, urgent actions are needed to reduce obesity and metabolic syndrome and improve FF's physical fitness. Our findings also support evidence-based recommendations to implement occupational health screening strategies for the early detection of FFs that would benefit from LOH and low TT treatment, both pharmacological and non-pharmacological, depending on each case. We would like to highlight the remarkable work that the Fire Service of Brasilia has been doing in this matter. Briefly, they have built a fitness center for every firefighter battalion, a medical occupation health screening every other year, and an annual mandatory physical fitness test that affects firefighters' promotion within the ranks. A thorough scientific investigation has not been completed, but our research group is currently investigating the effect of such policies on physical activity and obesity using longitudinal research.

Lastly, we summarize our findings and conclusions in figure 10. Due to the importance of CRF, it is in the center of the figure. In our study, CRF was an independent predictor of the FRS, and different CRF levels were associated with CV risk categories in the crude analysis. While BMI was not directly associated with CV risk in our analysis, explaining why it is not “central” in our figure like CRF, it is associated with LOH, MS, and hyperglycemia, all of which are CV-risk-related conditions. In our analysis, BMI also predicted TT levels, which were a predictor of FRS. BMI and CRF are also usually correlated, with weight loss sometimes happening in conjunction with CRF increase and weight loss resulting in better fitness in CRF tests, especially in those with obesity. Thus, we highlight in our schematic the importance of fitness for diminishing CV risk, directly or indirectly.

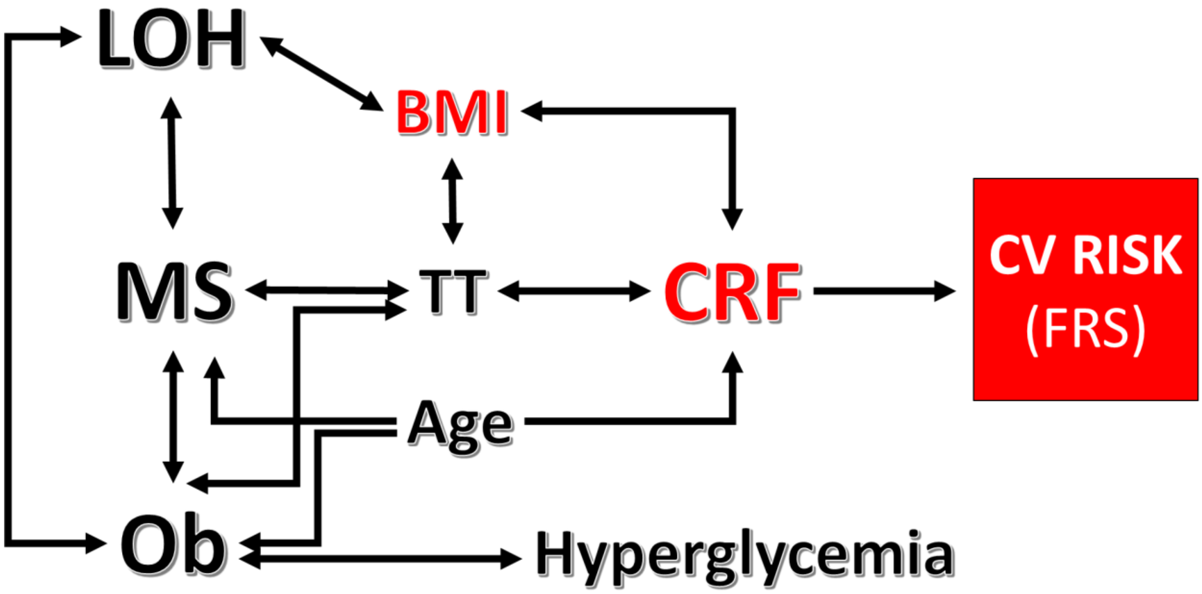

Figure 10. Schematic of our findings and conclusions showing the associations between different conditions and predictors variables. Cardiorespiratory fitness (CRF) and body mass index (BMI) are highlighted due to their direct or indirect relationship with cardiovascular (CV) risk and CV risk-related conditions and variables. Due to their bidirectional nature and the limitation of our study (cross-sectional), we utilized two-way arrows for almost all variables except for age.

8. OUTLINE OF THE WORK DONE DURING THE GRADUATE PROGRAM

Like all Brazilian Federal Universities, the University of Brasilia (UnB) has “the triad” as its cornerstone: research, teaching, and community service. It is possible to say that a graduate program would represent the research arm of this triad. However, teaching and community services are essential aspects of a Federal Public University. Therefore, doctoral students/candidates must lead the development of their primary research project alongside his/her mentor. In addition, it is expected that students engage in other research projects parallel to the main one, leading them or in collaboration, as well as in other university activities, especially teaching-related ones as teacher assistants or professors in training. Those mandatory and desirable requirements are strongly stimulated by the professors of the GEAFS study group (Research Group in Physiology and Epidemiology of Exercise and Physical Activity – GEAFS), linked to the Faculty of Physical Education of the University of Brasilia, where I did my graduate program. Also, one of the current UnB aims is to increase international collaboration. This aspect of the University values was also accomplished during my Ph.D. program by participating in a 6-month doctoral sandwich program in collaboration with Skidmore College, working under Prof. Denise Smith’s supervision, and participating in research projects in international collaboration.

It is essential to clarify that our Graduate Program (PPGEF) is currently reviewing the eligible Master and Doctoral thesis formats. A format based on scientific papers, along with a comprehensive introduction and discussion aiming to link the published scientific research related to the central research theme, has already been approved by UnB. However, the specific requirements for doing it in our Graduate Program still need to be established. Therefore, my advisor and I decided to present this thesis in the traditional monograph format presenting as the main product only the work related to my primary program goal, i.e., the prevalence of LOH, MS, and obesity among Brazilian firefighters and its associated factors. However, much more has been done, and the following summary must be considered as part of this Ph.D. thesis.

In this brief outline, we present the result of the work done during my Ph.D. program under these three University arms to give a more comprehensive overview of my full engagement during this period.

8.1. PEER-REVIEWED PUBLISHED RESEARCH

During the Ph.D. program, I, Edgard, have extensively worked in firefighter health, physical activity, and fitness research, which are research themes closely related to my main research area. This resulted in 9 papers published in peer-reviewed journals:

1.	Soares, E.M.K.V.K., Molina, G.E., Saint Martin, D., Leitão, J.L.A.E.S.P., Fontana, K.E., Junqueira, L.F., de Araújo, T.L., Matsudo, S.M., Matsudo, V.K., Porto, L.G.G.: **Questionnaire-Based Prevalence of Physical Activity Level on Adults According to Different International Guidelines: Impact on Surveillance and Policies**. J. Phys. Act. Health. 16 (11), 1014–1021 (2019)	Compares the impact of different criteria on physically active prevalence. This data helped us choose which criteria to use in our study and reflected in our interpretation of findings related to PA levels.
2.	Soares, E.M.K.V.K., Smith, D., Grossi Porto, L.G.: **Worldwide prevalence of obesity among firefighters: a systematic review protocol**. BMJ Open. 10 (1), e031282 (2020)	This is the protocol of our systematic review of obesity, which is currently being completed to be submitted as a new article. Designing and performing the study gave us a broader understanding of the FF obesity situation, which enriched our discussion in the thesis.
3.	Wilkinson, A.F., Matias, A.A., Eddy, C.I.K., Soares, E.M.K.V.K., King, J.L., Smith, D.L.: **Physiologic strain of SCBA confidence course training compared to circuit training and live-fire training**. Appl. Ergon. 82 102966 (2020)	Heart rate and temperature data were measured in three different situations in FFs. This work highlights the severe cardiac strain FFs go under, even in simulated exercises without a live fire. My participation in this paper was part of the work done during my “doctoral sandwich period” at Skidmore College under Prof. Smith's supervision.
4.	Martin, D.R.F.S., Segedi, L.C., Soares, E.M.K.V.K., Nogueira, R.M., Cruz, C.J.G., Fontana, K.E., Molina, G.E., Porto, L.G.G.: **Physical activity level and cardiovascular strain in military firefighters during wildland firefighting: an exploratory study**. Rev. Bras. Saúde Ocupacional. 45 (2020)	This is a paper resulting from a Master’s thesis of a member of our group. This work helped us visualize how active FFs are, especially in wildland firefighting.

5.	Segedi, L., Saint-Martin, D., Cruz, C., Soares, E.M.K.V.K., da Nascimento, N., da Silva, L., Nogueira, R., Korre, M., Smith, D., Kales, S., Molina, G., Porto, L.: **Cardiorespiratory fitness assessment among firefighters: Is the non-exercise estimate accurate?** WORK- J. Prev. Assess. Rehabil. 67 (1), 173–183 (2020)	This is a paper resulting from a Master's thesis of a member of our group. This work was very important to the thesis since the questionnaire we used was validated in FFs in this research.
6.	Lofrano-Porto, A., Soares, E.M.K.V.K., Matias, A., Porto, L.G.G., Smith, D.L.: **Borderline-low testosterone levels are associated with lower left ventricular wall thickness in firefighters: An exploratory analysis.** Andrology. 8 (6), 1753–1761 (2020)	This paper celebrates our partnership/collaboration with Skidmore College. This collaboration was fostered by the development of our main research project on FFs' health, of which my thesis project is part and has my mentor as its principal investigator. We investigated the relationship between left ventricular wall thickness and serum TT levels. This paper strongly contributes to this thesis, especially as the first research on FFs and low testosterone.
7.	Porto, L.G.G., Molina, G.E., Saint Martin, D.R.F., Soares, E.M.K.V.K., Barbosa, J.P.A., Barreto, K.A., da Cruz, C.J.G., Nogueira, R.M.: **Bombeiro militar e saúde: práticas e desafios – uma perspectiva do grupo de estudos em fisiologia e epidemiologia do exercício e da atividade física (GEAFS)**. Rev. FLAMMAE. 06 (16), 7–38 (2020)	This paper includes a review of our work, research, and collaboration with the Fire Service. This work addresses the importance of cardiorespiratory fitness and body composition.
8.	Nogueira, R.M., Saint-Martin, D.R.F., Soares, E.M.K.V.K., Barbosa, J.P.A., Barreto, K.A., Silva, M. de C., Segedi, L.C., Cruz, C.J.G. da, Garcia, G.L., Barbosa, W.G., Molina, G.E., Porto, L.G.G.: Risco cardiovascular e o papel da aptidão física para o bombeiro militar/ **Cardiovascular risk and the role of physical fitness for the military fireman**. Rev. SUSP. 1(1) 113-132 (2021)	This paper reviews the importance of cardiorespiratory fitness and adequate body composition in FF health and occupational performance. This helped reinforce the importance of fitness to estimate cardiovascular risk in FFs.
9.	Ranadive, S.M., Lofrano-Porto, A., Soares, E.M.K.V.K., Eagan, L., Porto, L.G.G., Smith, D.L.: **Low testosterone and cardiometabolic risks in a real-world study of US male firefighters**. Sci. Rep. 11 (1), 1–10 (2021)	In a new analysis, we investigate the association between cardiometabolic risk factors and low TT. The findings from this study were significant in the design and planning of our data analysis.

Due to my exercise physiology background and as a member of the GEAFS research group, I have contributed to other 8 papers in the field of ergogenic aid, systematic review, heart rate variability, and exercise training. Significantly, our research group has also been interested in the role of the cardiac autonomic system (CAS) of the cardiovascular on FF's health and/or the effects of FF's duty-related activities on CAS. Depending on the paper, my contribution was either on exercise physiology, research methods, or biostatistics:

1. da Silva Rolim, P., da Costa Matos, R.A., Soares, E.M.K.V.K., Molina, G.E., da Cruz, C.J.G.: **Caffeine increases parasympathetic reactivation without altering resting and exercise cardiac parasympathetic modulation: A balanced placebo design**. Eur. J. Sport Sci. 19 (4), 490–498 (2019)
2. Mafra, R., Ferreira, C.E.S., Soares, E.M.K.V.K., Carvalho, F.O., Madrid, B.: Massa muscular estimada por diferentes equações antropométricas**/ Estimating muscle mass using various anthropometric equations**. Rev. Bras. Ciênc. E Mov. 26 (1), 5–12 (2018)
3. Soares, E.M.K.V.K., Garcia, G.L., Molina, G.E., Fontana, K.E.: **Muscle strength and caffeine supplementation: are we doing more of the same?** Rev. Bras. Med. Esporte. 25 168–174 (2019)
4. Morlin, M.T., Cruz, C.J.G. da, Melo, P.B.S., Lopes, G.H.R., Soares, E.M.K.V.K.., Porto, L.G.G., Molina, G.E.: **Bradycardia in athletes: does the type of sport make any difference? – a systematic review**. Rev. Bras. Med. Esporte. 26 449–453 (2020)
5. Molina, G.E., da Cruz, C.J.G., Fontana, K.E., Soares, E.M.K.V.K., Porto, L.G.G., Junqueira, L.F.: **Post-exercise heart rate recovery and its speed are associated with cardiac autonomic responsiveness following orthostatic stress test in men.** Scand. Cardiovasc. J. 55 (4), 220–226 (2021)
6. Giuriato, G., Venturelli, M., Matias, A., Soares, E.M.K.V.K., Gaetgens, J., Frederick, K.A., Ives, S.J.: **Capsaicin and Its Effect on Exercise Performance, Fatigue and Inflammation after Exercise.** Nutrients. 14 (2), 232 (2022)
7. Santos, T.M.L., Molina, G.E., Guimarães, F.E.R., Cruz, C.J.G. da, Carminatti, L.J., Soares, E.M.K.V.K.: Avaliação do pico de velocidade no teste de Carminatti (T-CAR) em jogadores de futebol da segunda divisão, no início, e no fim de uma pré-temporada/ **Evaluation of the peak velocity in Carminatti's test (T-CAR) in the start, and end of a preseason of second division soccer players.** RBFF - Rev. Bras. Futsal e Futeb. 13 (56), 726–737 (2021)
8. Barbosa, W.G., Saint Martin, D.R., Soares, E.M.K.V.K., Fontana, K.E., Lan, F.-Y., Kales, S.N., Molina, G.E., Porto, L.G.G.: **The effects of a 6-month mandatory military police academy training on recruits' physical fitness**. Work. Preprint (Preprint), 1–10 (2022)

8.2. ARTICLES IN-WRITING AIMED AT PEER-REVIEWED JOURNALS

I am also currently working on three different papers, all as the first author. These papers are essential to our main line of research and directly related to the thesis. The first is investigating the association between FF's testosterone levels and fitness, a continuation of our previous work 6, 9. based on US FFs data and in collaboration with Dr. Smith's Lab. We are also in the final stages of writing our systematic review on worldwide FFs´ obesity prevalence (SOARES; SMITH; PORTO, 2020). Finally, we are working on preparing the paper related to the results presented in this thesis. Due to a large amount of data and valuable information, this will probably result in more than one article. There is another paper in which I am a collaborator, which is currently under review. Its data is also related to a broad research theme, i.e., FF´s health, as it is a longitudinal analysis of BMI and CRF change over the years in the Fire Service.

It is also important to highlight that we are currently concluding two intervention projects aiming to improve FF´s health. One is the Master's degree project of a student that works under my co-mentoring with Prof. Porto and results directly from this thesis. We are investigating the effect of three months of lifestyle intervention on FFs' testosterone and traditional cardiometabolic risk factors among FFs who presented TT levels <400 ng/dL in the prevalence study. Data collection has finished, and we are now in the analysis phase. The second one is the main part of the Ph.D. program of another Ph.D. candidate under Prof. Porto's mentoring and with whom I have worked closely. In this project, we will evaluate five months of a comprehensive lifestyle intervention (exercise, physical activity, diet, and sleep) on traditional and novel cardiovascular risk factors within all members of one Brasilia Fire Battalion as a pilot intervention. This project is an initiative of the Brasilia Fire Department, to which we were invited to perform scientific monitoring. Depending on the results, the intervention might be expanded to other Brasília Fire Battalion. We are currently concluding the post-intervention data collection.

8.3. NON-PEER-REVIEWED PUBLISHED RESEARCH

During the graduate program, I have collaborated on over 50 conference papers involving our research theme: firefighter health, testosterone, fitness, and physical activity. Two of the conference papers received honorable mentions in the symposiums they were presented, and one was awarded the Actigraph best scientific investigation award in 2017. I want to highlight two of them that are partial results of our research. They are data from the 2020 part of this research that also helped our understanding of this phenomenon and nourished future hypotheses of our complete study. Our findings reinforced the importance of cardiorespiratory fitness to cardiometabolic risk and serum total testosterone levels. Both were presented in international symposiums in a virtual format due to the COVID-19 pandemic.

1. Soares, E.M.K.V.K., Saint-Martin, D.R., Barreto, K.A., Nogueira, R.M., Molina, G.E., Smith, D.L., Lofrano-Porto, A., Grossi Porto, L.G.: **Cardiorespiratory Fitness Vs. Fatness: An Exploratory Study On Firefighters' Cardiometabolic Health And Serum Testosterone**. In: ACSM's 68th Annual Meeting, 2021, Online event. Available at: Med. Sci. Sports Exerc. 53 (8S), 363 (2021).
2. Soares, E.M.K.V.K.; Saint-Martin, D.R, Barreto, K.A.; Nogueira, R.M., Molina, G.E., Smith, D.L., Lofrano-Porto, A., Grossi Porto, L.G.: **Serum Total Testosterone in Brazilian Male Firefighters: An exploratory study of its relationship with physical fitness and cardiovascular risk**. In: 43o. Simpósio Internacional de Ciência do Esporte - CELAFISCS, 2020, Online event. Available at: Suplemento RBCE, 2020. v. 29 (1), 150 (2020).

Lastly, I would like to call attention to a book chapter in which I am the first author, along with my advisor, Prof. Porto, and Prof. Molina, entitled "Teaching Statistics in Exercise Science – a case study accompanied by a narrative review on active learning strategies." This work is celebrated in this thesis not only because of its content but because of its symbolism. The case study is an analysis and report of teaching methods and strategies implemented during my time as a "substitute professor" at the UnB – a visiting assistant professor who teaches courses for full professors on leave. The methods, strategies, and program reflect what I lived and experienced throughout the Ph.D. program. The "Statistics Applied to Exercise Science" course went from one with the highest failure rates to one with a success rate of 94% despite adding new content like basic inferential statistics.

Soares, E.M.K.V.K., Molina, G.E., Grossi Porto, L.G.: Ensino de Estatística em um curso de Educação Física – um estudo de caso acompanhado de revisão narrativa sobre estratégias pedagógicas ativas/**Teaching Statistics in Exercise Science – a case study accompanied by a narrative review on active learning strategies**. In: Metodologias e Tecnologias de Apoio a Processos Educacionais em Transformação. pp. 81–118. (2022)

8.4. FUNDING

The funding for this research was awarded in a grant won by my advisor Prof. Porto. The Fundação de Apoio a Pesquisa do Distrito Federal (FAPDF) funded our research. Also, I have been awarded two grants from the Dean of Post-Graduation of the UnB to support costs with data collection. I have also been awarded a travel grant from FAPDF to present a conference paper.

One of the most critical funding obtained was from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Higher Education in Brazilian Federal Universities is free. Still, CAPES has a unique funding program to support those who wish to commit themselves full-time to the Ph.D. program by paying a monthly scholarship. Despite its importance, recent political changes in the Brazilian educational budget have made this type of funding even more scarce. Obtaining this scholarship from CAPES is a source of pride among Ph.D. students.

The second significant funding was also from CAPES, who awarded me a scholarship for the doctoral sandwich period, covering expenses that allowed me to work for six months under Prof. Smith's supervision at the First Responder Health and Safety Laboratory – Skidmore College.

While working under Prof. Smith, I was able to contribute to significant research, published and in-written as mentioned previously, and I also had the opportunity to contribute to two grant proposals for a testosterone and Fire Service research line, which has not yet been funded but resulted in remarkable academic growth and research opportunities.

8.5. TEACHING

Brazilian Ph.D. programs include teaching internship courses, which are obligatory for those funded by CAPES. As so, I have performed a one-year teaching internship under Prof. Porto in the "Epidemiology Applied to Physical Education" discipline of the undergraduate course. I also was a peer tutor for the "Epidemiology and Physical Activity in Health Promotion," also under Prof. Porto, which is a discipline of the graduate course (available to those doing their Master's or Ph.D. program).

During the Ph.D. program, I was also approved for a Substitute Professor position at the University of Brasilia (UnB). I was responsible for the "Statistics Applied to Physical Education" and "National Sports Methodology." To be approved for such a position in Brazil, it is necessary to perform a civil servant exam which is highly competitive due to the small number of jobs available compared to the number of applicants. Specifically, in this exam, the curriculum is the main criterion.

I was also selected as a Professor for the Open University of Brazil (UAB – Portuguese acronym) at the UnB. UAB aims to offer the same high-quality education provided by the UnB but through distance learning. This program is aimed at regions of Brazil that generally do not have access to higher education. I taught "Exercise Physiology II" and "Metrics and Fitness Evaluation in Exercise Science."

8.6. COMMUNITY SERVICES

As a part of our desire to "give back" to society, and as a member of the GEAFS, I worked alongside the organizers of the 1st, 2nd, and 3rd International Symposium on Health and Physical Fitness among Public Safety Workers (SISAF – Portuguese acronym). I was also a speaker at the 2nd and 3rd SISAF. I also worked with other research group members on organizing a series of events called "Coffee with GEAFS" to bridge the gap between exercise science research, undergraduate students, and the general public. I also gave two lectures on evidence-based exercise prescription at one of the Fire Service headquarters, as requested by them.

8.7. CLOSING STATEMENT

This quick outline summarizes the output of the years working under Prof. Porto during the Ph.D. program. The University of Brasilia values the enrichment of its human resources, and as important as research, teaching, and community services outcomes are, words are insufficient to perfectly express the growth and life experience of the last years. Almost uncountable hours of work and dedication are imbued in what is presented in this outline and the thesis' work as a whole. Long conversations leading to personal and professional growth are a part of this. The experience of working abroad under the tutelage of Prof. Smith would also require a book of its own. All of this was possible thanks to our University, FAPDF, and CAPES.

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ANNEX I - IPAQ

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
SHORT VERSION - (9th version)

The questions are related to the time you spent doing physical activity in the **LAST week**. Questions include activities you do at work, to get from place to place, for leisure, sport, exercise, or as part of your activities at home or in the garden.

- To answer the questions remember that:
- VIGOROUS physical activities are those that require great physical effort and make you breathe MUCH harder than normal.
- MODERATE physical activities are those that require some physical effort and make you breathe A LITTLE harder than normal.

To answer the questions, just think about the activities you do **for at least 10 continuous minutes** at a time:

1st On how many days in the last week did you **WALK** for at least 10 continuous minutes at home or at work, as a form of transport to get from one place to another, for leisure, for pleasure or as a form of exercise?

_______days per **WEEK** ☐ None

1b. On days when you walked for at least 10 continuous minutes, how much time in total did you spend walking **per day** ?

hours:_________minutes:________

2nd On how many days in the last week did you perform **MODERATE activities** for at least 10 continuous minutes , such as light cycling, swimming, dancing, light aerobics, recreational volleyball, light weight lifting, housework, yard or garden such as sweeping, vacuuming, gardening, or any activity that **moderately increased** your breathing or heart rate **(PLEASE DO NOT INCLUDE WALKING).**

_______days per **WEEK** ☐ None

2b . On days when you did these moderate activities for at least 10 minutes at a time, how much time in total did you spend doing these activities **per day** ?

hours:_________minutes:________

3a. On how many days in the past week have you performed **VIGOROUS activities** for at least 10 continuous minutes , such as running, aerobics, playing soccer, fast cycling, playing basketball, doing heavy housework at home, in the yard, or digging in the garden, carrying heavy weights, or any activity that made your **breathing** or heart rate HUGE.

_______days per **WEEK** ☐ None

3b. On days when you did these vigorous activities for at least 10 continuous minutes, how much time in total did you spend doing these activities **per day** ?

Hours: ________Minutes:________

ANNEX II - SRPA

SELF-REPORTED PHYSICAL ACTIVITY QUESTIONNAIRE

Please select below **ONLY ONE NUMBER** that best represents your overall physical activity in the last month.

I DO NOT PARTICIPATE REGULARLY IN PROGRAMMED LEISURE ACTIVITIES, SPORTS OR VIGOROUS PHYSICAL ACTIVITIES.

0 – I avoid walking or physical exertion (for example, I always use elevators and drive whenever possible, instead of walking, cycling or skating).

1 – I walk for pleasure, usually use the stairs, occasionally exercise enough to pant or sweat.

I REGULARLY PARTICIPATE IN LEISURE OR WORK ACTIVITIES THAT REQUIRE MODERATE PHYSICAL ACTIVITY, SUCH AS PLAYING GOLF, HORSEBACK RIDING, CALISTHENICS, GYMNASTICS, TABLE TENNIS, BOWLING, WEIGHT LIFTING OR GARDENING.

2 – 10 to 60 minutes per week.

3 – more than one hour per week.

I REGULARLY PARTICIPATE IN VIGOROUS PHYSICAL EXERCISES SUCH AS RUNNING, JOGGING, SWIMMING, CYCLING, ROWING, ROPE SKIPPING, TREADMILL OR STRONG AEROBIC EXERCISES SUCH AS TENNIS, BASKETBALL, HANDBALL, VOLLEYBALL OR FOOTBALL.

4 – I run less than 1.6 km per week or spend less than 30 minutes per week in physical activity of similar intensity.

5 – I run between 1.6 to 8 km per week or spend between 30 and 60 minutes per week in physical activity of similar intensity.

6 – I run between 8 and 16 km a week or spend between 1 and 3 hours a week in physical activity of similar intensity.

7 – I run more than 16 km a week or spend more than 3 hours a week in physical activity of similar intensity.

ANNEX III - ADAM

University of St. Louis – Androgen Deficiency in the Aging Male questionnaire (ADAM)

Mark "yes" or "no" for each of the questions below:

Questions	Yes	No
1) Do you have a decrease in libido (sex drive)?		
2) Do you have a lack of energy?		
3) Have you felt a decrease in strength and/or physical endurance?		
4) Have you noticed a decrease in your height?		
5) Have you observed a decrease in "enjoyment of life"?		
6) Have you been sad or in a bad mood for no apparent reason?		
7) Do you think your erections have been less strong?		
8) Have you noticed a recent deterioration in your ability to play sports?		
9) Have you been feeling very sleepy after dinner?		
10) Has there been a recent deterioration in your work performance?		

ANNEX IV - PSQI

Pittsburgh Sleep Quality Index (PSQI)

The following questions pertain to your sleep habits **during the last month only.** Your answers should indicate the most accurate recollection of **most** days and nights in the last month . Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

Usual bedtime ___________________

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

Number of minutes ___________________

3. During the past month, what time have you usually gotten up in the morning?

Usual time to get up ____________________

4. During the past month, how many hours of **actual sleep** did you get at night? (This may be different from the number of hours you spent in bed).

Hours of sleep per night _________

For each of the remaining questions, mark the **best (one)** answer. Please answer all questions

5. During the past month, how often have you **had difficulty sleeping** because you...

(a) Failed to fall asleep within 30 minutes

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(b) Woke up in the middle of the night or early in the morning

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(c) Had to get up to go to the bathroom

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(d) Could not breathe comfortably

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(e) coughed or snored loudly

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(f) Felt very cold

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(g) Felt very hot

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(h) Had bad dreams

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(i) Had pain

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

(j) Other reason(s), please describe ________________________________

How often during the past month have you had trouble sleeping for this reason?

1 = Not in the last month 2 = Less than once a week

3 = Once or twice a week 4 = Three or more times a week

6. Over the past month, how would you rate your sleep quality in general?

1 = Very good 2 = Fairly good 3 = Fairly Bad 4 = Very bad

7. During the past month, how often have you taken medication (prescription or "on your own") to help you sleep?

1 = none in the last month 2 = less than once a week

3 = once or twice a week 4 = three or more times a week

8. In the last month, how often have you had difficulty staying awake while driving, eating or participating in a social activity (party, meeting with friends, work, studying)?

1 = none in the last month 2 = less than once a week

3 = once or twice a week 4 = three or more times a week

9. During the past month, how much of a problem has it been for you to maintain your enthusiasm (momentum) to get things done (your usual activities)?

1= No problem at all 2 = Fairly good

3 = Fairly bad 4 = Very bad

ANNEX V (WHOQOL-Bref)

Quality of Life Questionnaire: WHOQOL-Bref

Please read each question, see what you think and circle the number that seems to be the best answer.

		Very poor	Poor	neither poor nor good	Good	Very good
1	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2	How satisfied are you with your health?	1	2	3	4	5

The following questions are about **how much** you have been feeling certain things in the **last two weeks** .

		Not at all	A little	Moderate amount	Very much	Extremely
3	To what extent do you think your (physical) pain prevents you from doing what you need to do?	1	2	3	4	5
4	How much do you need any medical treatment to get on with your daily life?	1	2	3	4	5
5	How much do you enjoy life?	1	2	3	4	5
6	To what extent do you think your life has meaning?	1	2	3	4	5
7	How much can you concentrate?	1	2	3	4	5
8	How secure do you feel in your daily life?	1	2	3	4	5

9	How healthy is your physical environment (weather, noise, pollution, attractions)?	1	2	3	4	5

The following questions ask about **how fully** you have been feeling or able to do certain things in the **past two weeks** .

		Not at all	A little	Moderately	Mostly	Completely
10	Do you have enough energy for your daily life?	1	2	3	4	5
11	Are you able to accept your physical appearance?	1	2	3	4	5
12	Do you have enough money to satisfy your needs?	1	2	3	4	5
13	How available to you is the information you need in your daily life?	1	2	3	4	5
14	To what extent do you have leisure activity opportunities?	1	2	3	4	5

The following questions ask **how well or satisfied** you have felt about various aspects of your life in the **past two weeks** .

		Very poor	Poor	Neither poor nor good	Good	Very good
15	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16	How satisfied are you with your sleep?	1	2	3	4	5
17	How satisfied are you with your ability to perform your	1	2	3	4	5

	day-to-day activities?					
18	How satisfied are you with your ability to work?	1	2	3	4	5
19	How satisfied are you with yourself?	1	2	3	4	5
20	How satisfied are you with your personal relationships (friends, relatives, acquaintances, colleagues)?	1	2	3	4	5
21	How satisfied are you with your sex life?	1	2	3	4	5
22	How satisfied are you with the support you receive from your friends?	1	2	3	4	5
23	How satisfied are you with the conditions where you live?	1	2	3	4	5
24	How satisfied are you with your access to health services?	1	2	3	4	5
25	How satisfied are you with your means of transport?	1	2	3	4	5

The following questions ask **how often** you have felt or experienced certain things in the **last two weeks** .

		Never	Seldom	Quite often	Very often	Always
26	How often do you have negative feelings such as moodiness, despair, anxiety, depression?	1	2	3	4	5