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The "obesity paradox" in an elderly population with a high prevalence of Chagas disease: The 10-year follow-up of the Bambuí (Brazil) Cohort Study of Aging

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Chagas disease (ChD) affects approximately 10 million individuals in Latin America and, due to immigration it is also of increasing importance in North America and Europe. Chronic cardiomyopathy, observed in 20–40% of the cases, is the most important and lethal complication of ChD [1]. Control of the transmission by the use of insecticides and aging of the individuals infected in early adulthood are making ChD a health burden in the elderly in old endemic areas. As the prevalence of overweight/obesity in this age group has been increasing, the two conditions are likely to co-exist in older individuals [2].

The "obesity paradox" (i.e., longer survival of overweight/obese individuals in comparison to lean ones) has been described in older adults with and without cardiovascular diseases (CVD) [3]. The etiology of heart disease (HD) might have influence on the phenomenon [4]. Whether overweight/obesity are protective determinants of mortality in subjects with Chagas disease (ChD) is still unknown.

Our aim was to investigate the relationship between body mass index (BMI), waist circumference (WC) and death, in relation to heart disease (HD), among elderly participants with a high prevalence of ChD in the Bambuí (Brazil) Cohort Study of Aging (BHAS).

The BHAS, a cohort study of elderly residents in the Bambuí City (Minas Gerais, southeast of Brazil) is described in detail elsewhere [5], and was approved by the ethics board of the Fundação Oswaldo Cruz, Belo Horizonte, Brazil. An informed consent form was obtained from all participants. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing.

The outcome of the present analysis was overall death from baseline (1997) to 2007. *Trypanosoma cruzi* infection, anthropometric measurements (AM) assessment, B-type natriuretic (BNP) test, and definitions of other measurements performed were detailed previously [5]. AM were repeated in the surviving participants in 2000 and 2002. Underweight (BMI<18.5 kg/m^2; n = 104; 7.2%) subjects were excluded. ECGs were codified according to the Minnesota code (MC) [6] and classified as abnormal in the presence of major abnormalities [7] or of frequent supraventricular and ventricular premature beats (MC 8.1.1, 8.1.2 or 8.1.3). HD was defined by the combination of an abnormal ECG and augmented BNP levels. As BNP levels are inversely related to BMI and WC levels in the BHAS [8], we used distinct cut-off points according to BMI classification: 106 pg/mL in the normal and 128 pg/mL in the high BMI group.

Survival rates were compared across the groups formed according to HD status, and to normal (18.5≤BMI<25 kg/m^2) or high BMI (BMI≥25 kg/m^2), and low (<88 cm for women, <102 cm for men) or high WC (≥88 cm for women, ≥102 cm for men) by Kaplan–Meier (KM) curves and log-rank tests. Overall, 7.2% of all values were missing. We performed multiple imputation of missing values with generation of five complete datasets [9]. Hazard ratios (HR) and 95% confidence intervals (CI) of death according to BMI/WC (continuous) at various time-points were estimated by extended Cox regression models [10]. Each model was additionally adjusted for a set of demographic, clinical, socioeconomic and behavioral determinants of death, as well as for a product term of interaction between BMI/WC and HD status. Subsequently, we stratified by ChD, and excluded subjects with probable cachexia (≥10% weight loss weight and death within the first five years of follow-up). Absolute rates of death *per* unit of BMI were estimated by KM curves.

After exclusions and losses to follow-up (78; 5.8%), 1271 participants entered the analysis, 208 (16.4%) of whom had HD. These were older (70.4, SD: 6.7 versus 68.1, SD: 7.2 years; p = 0.003) and had a higher prevalence of ChD (137, 65.9% versus 320, 30.0%; p<0.001). Differences between the groups with and without HD in relation to BMI status are depicted in Table 1.

Mean follow-up time was 9.0 years. Deaths occurred in 128 (61.5%) and 310 (29.2%) subjects with and without HD, respectively. High BMI/WC were associated with the lowest survival rates at 10-year follow-up regardless of HD status (Figs. 1 and 2). After full adjustment, the relationship between mortality and BMI and WC, was U-shaped and non-significant, respectively. These results were similar after exclusion of participants with probable cachexia, and regardless of HD and ChD

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Table 1
Baseline characteristics, according to groups with and without HD and with normal or high BMI levels.

Characteristics	Without HD (n 1063; 83.6%)			With HD (n 208; 16.4%)		
	Normal BMI (478; 37.6%)	Normal BMI (585; 46.0%)	Differences* (95% CI)	Normal BMI (107; 8.4%)	High BMI (101; 7.9%)	Differences* (95% CI)
Age† (years)	68.7 (7.0)	67.7 (6.5)	1.0 (0.2, 1.8)	71.6 (7.6)	69.0 (6.5)	2.6 (0.7, 4.5)
Female sex‡	252 (51.6)	403 (68.1)	−16.5% (−22.2, −10.6)	55 (51.4)	75 (74.3)	−22.9% (−35.6, −10.1)
BMI (kg/m^2)§	22.6 (20.9, 23.8)	28.2 (26.5, 30.5)	–	21.9 (20.6, 23.4)	27.7 (26.4, 29.5)	–
BMI (kg/m^2)†	22.3 (1.7)	29.1 (3.8)	−6.7 (−7.1, −6.5)	22.0 (1.8)	28.7 (3.7)	−6.7 (−7.5, −5.9)
WC (cm)	86 (7.1)	99 (9.1)	−13.0 (−14.0, −12.1)	85.2 (6.6)	98.9 (8.4)	−13.7 (−15.7, −11.8)
Chagas disease‡	161 (33.7)	157 (26.8)	6.9% (1.3, 12.4)	79 (73.8)	58 (57.4)	16.4% (3.7, 29.1)
Smoking‡	106 (22.2)	58 (9.9)	12.3% (7.8, 16.7)	26 (24.3)	10 (9.9)	14.4 (4.4, 24.4)
BNP (pg/dL)§	66.0 (38, 113)	59.0 (32, 97)	–	225.0 (162, 321)	189.0 (139, 265)	–
BNP (pg/dL)†	100.8 (137.4)	88.2 (118.0)	12.6 (−3.0, 28.2)	305.8 (268.5)	258.5 (234.5)	47.3 (−21.1, 115.7)
CRP (mg/dL)§	2.31 (1.06, 4.92)	3.94 (1.84, 6.88)	–	3.15 (1.27, 7.29)	4.94 (2.30, 8.66)	–
CRP (pg/dL)†	4.73 (9.39)	6.01 (10.12)	−1.3 (−2.5, −0.1)	5.82 (8.33)	8.09 (1.20)	−2.3 (−5.0, 0.4)
Systolic blood pressure (mm Hg)†	136 (23)	138 (20)	−2.4 (−5.0, 0.3)	141 (26)	144 (26)	−3.8 (−10.8, 3.2)
Diabetes mellitus‡	47 (9.9)	117 (20.0)	−10.1% (−14.3, −5.9)	11 (10.3)	19 (18.8)	−8.5% (−18.1, 1.0)
Digoxin use‡	53 (11.1)	75 (12.8)	−1.7% (−5.6, 2.2)	27 (25.2)	23 (22.8)	2.4% (−9.1, 14.1)
Anti-hypertensive medication use‡	176 (36.8)	360 (61.5)	−24.7% (−30.6, −18.9)	59 (55.1)	69 (68.3)	−13.2% (−26.3, −0.1)
Serum creatinine (mg/dL)§	0.85 (0.75, 0.97)	0.83 (0.73, 0.97)	–	0.90 (0.79, 1.09)	0.90 (0.79, 1.08)	–
Serum creatinine (mg/dL)†	0.90 (0.35)	0.86 (0.20)	−0.02 (−0.07, 0.00)	0.99 (0.49)	0.95 (0.29)	0.00 (−0.08, 0.14)
Total cholesterol (mg/dL)†	231 (49)	239 (49)	−7.9 (−13.8, −1.9)	233 (53)	234 (47)	−0.8 (−14.3, 12.8)
Physically active‡	98 (20.2)	156 (26.4)	−6.2% (−11.3, −1.2)	19 (17.8)	21 (20.8)	−3.0% (−13.8, 7.7)
Family income‡						
Lower	337 (69.9)	342 (58.4)	11.5% (5.8, 17.3)	84 (78.5)	78 (77.2)	1.3% (−10.0, 12.6)
Intermediate	110 (22.8)	176 (30.0)	−7.2% (−12.5, −1.9)	19 (17.8)	19 (18.8)	−1.1% (−11.6, 9.5)
Higher	35 (7.3)	68 (11.6)	−4.3% (−7.8, −0.9)	4 (3.7)	4 (4.0)	−0.2% (−5.5, 5.0)
Education‡						
Lower	160 (32.9)	128 (21.6)	11.3% (6.0, 16.6)	50 (46.7)	41 (40.6)	6.1% (−7.3, 19.6)
Intermediate	278 (57.2)	368 (62.2)	−5.0% (−10.8, 0.9)	52 (48.6)	55 (54.5)	−5.9% (−19.4, 7.7)
Higher	48 (9.9)	96 (16.2)	−6.3% (−10.3, −2.4)	5 (4.7)	5 (5.0)	−0.3% (−6.1, 5.5)

HD heart disease; BMI body mass index; WC waist circumference; BNP B-type natriuretic peptide; CRP C-reactive protein.
*Differences between means and proportions; continuous variables are described by means (SD)† or median (IQR)§ and categorical variables by frequencies (%)‡.

status (Table 2). BMI between 30 and 32 kg/m^2 was associated with the lowest absolute mortality rates at 10-year follow-up in participants with (46–47%) and without HD (20–21%).

Our results are similar to studies which found a protective role of overweight/obesity in the prognosis of subjects with HD [4,11]. Regarding the association between WC and mortality, previous findings in populations with HF are heterogeneous [12,13]. Not only high BMI being a marker of greater muscle mass, but also benefits associated with high fat mass, such as an increased strength capacity can explain these findings [14]. Neither reverse causation due to cachexia in elderly with normal BMI nor neutralization of the inflammatory effects of tumor necrosis factor (TNF)-alpha by soluble receptors in the adipose tissue [3] seems plausible explanations to our results, as suggested by the sensitivity analysis and by the highest CRP levels in subjects with both high BMI and HD, respectively. A healthier status of overweight/obese in comparison to lean subjects was not observed either.

Our study is unique in investigating the "obesity paradox" in older adults with ChD. The use of both BMI and WC directly measured at various time-points, the exclusion of subjects with underweight and probable cachexia, the long-term follow-up with minimal number of losses, and the high rate of events are major strengths. Limitations due to the small number of subjects with BMI ≥ 40 kg/m^2 (12; 1.1%), and to the lack of