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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

Alline Maria Beleigoli [a,*], Antonio Luiz Ribeiro [a,b], Maria de Fátima H. Diniz [a,b], Maria Fernanda Lima-Costa [a,c], Eric Boersma [d]

[a] *Faculdade de Medicina, Universidade Federal de Minas Gerais, Av. Alfredo Balena, 190-Belo Horizonte, CEP 30130-100, Brazil*
[b] *Hospital das Clínicas, Universidade Federal de Minas Gerais, Av. Alfredo Balena, 110-Belo Horizonte, CEP 30130-100, Brazil*
[c] *Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz, Av. Augusto de Lima, 1715-Belo Horizonte, CEP 30190-002, Brazil*
[d] *Erasmus Medical Center, Department of Cardiology, room Bd38,'s Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*

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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 ($18.5 \leq$ 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 ($\geq 10\%$ 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

* Corresponding author at: Rua Rogério Fajardo, 180/401, CEP 30310-450, Belo Horizonte, MG, Brazil. Tel.: +55 31 32851491; fax: +55 31 32233328.
E-mail address: beleigoli@yahoo.com (A.M. Beleigoli).

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
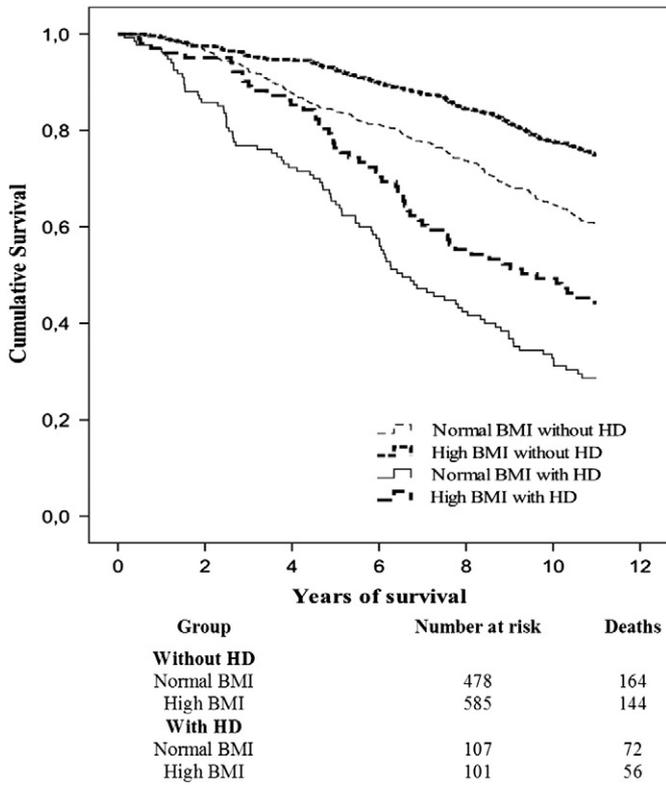
Fig. 1. Comparison of survival rates among groups with and without heart disease (HD), according to normal/high body mass index.
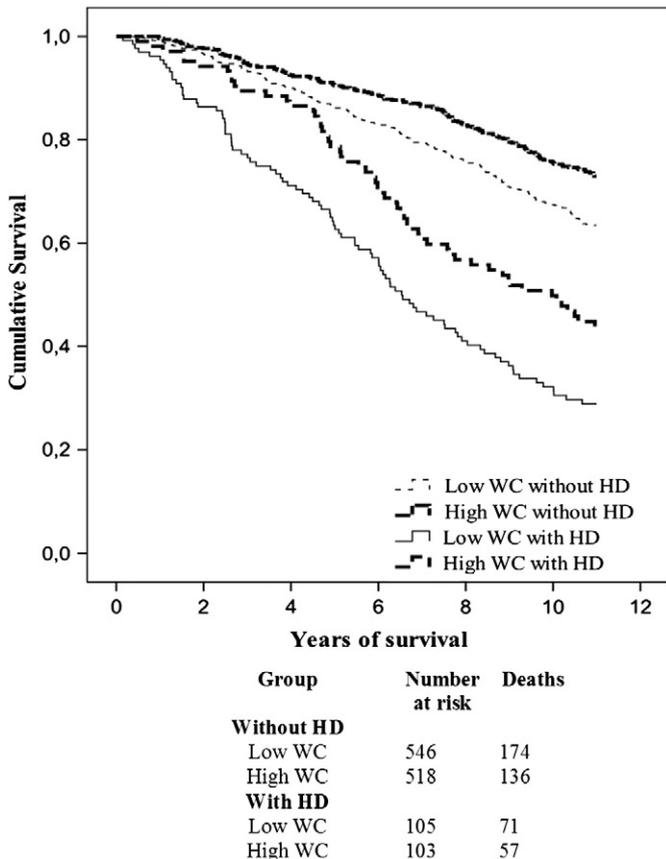
Group	Number at risk	Deaths
Without HD		
Normal BMI	478	164
High BMI	585	144
With HD		
Normal BMI	107	72
High BMI	101	56

Table 2

Hazard ratios (HR) and 95% confidence intervals (95% CI) for mortality related to BMI and WC in the overall population and in the subgroups of interest.

Anthropometric measures	HR (95% CI)		p value for interaction between HD and the anthropometric measure
	Unadjusted[a]	Fully adjusted[b]	
All participants			
BMI	0.77 (0.73–0.82)	0.82 (0.76–0.88)	0.48
WC	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.60
Participants with ChD			
BMI	0.65 (0.52–0.83)	0.70 (0.54–0.89)	0.13
WC	0.99 (0.98–1.01)	1.00 (0.99–1.01)	0.94
Participants without ChD			
BMI	0.77 (0.70–0.84)	0.79 (0.72–0.87)	0.22
WC	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.22
Participants without weight loss or early death			
BMI	0.82 (0.76–0.89)	0.88 (0.81–0.96)	0.98
WC	1.00 (0.99–1.02)	1.01 (0.99–1.02)	0.99

BMI body mass index; WC waist circumference; HD heart disease; ChD Chagas disease.
[a] Unadjusted: the BMI quadratic term is included in BMI models (HR not shown).
[b] Fully-adjusted: BMI and BMI square/WC plus age (continuous), sex, HD (no, yes), ChD (no, yes), current smoking (no, yes), diabetes (no, yes), total cholesterol (continuous), log-transformed creatinine (continuous), log-transformed C-reactive protein (continuous), physical activity (no, yes), household income, education (low, intermediate, high).

Fig. 2. Comparison of survival rates among groups with and without heart disease (HD), according to low/high waist circumference (WC).

Group	Number at risk	Deaths
Without HD		
Low WC	546	174
High WC	518	136
With HD		
Low WC	105	71
High WC	103	57

more accurate measurements of fat mass and left ventricle ejection function warrant mention.

In conclusion, high BMI levels are associated with higher survival regardless of HD status in an elderly population with a high prevalence of ChD, whereas high WC values do not influence on mortality. The "obesity paradox" should be taken into account when weight control is planned for elderly subjects with HD and ChD.

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How much does AVR ST change help stratify patients with coronary disease?

Cheuk-Kit Wong *

Department of Cardiology, Dunedin School of Medicine, University of Otago, Dunedin Public Hospital, New Zealand

A R T I C L E   I N F O

Lead aVR is recorded with positive input from the right arm electrode and negative input averaged from the left arm and left leg electrodes. It is arithmetically and geometrically reciprocal to standard leads I and II combined. Interpretation of aVR's unique orientation (with no contiguous lead) has been controversial. In the Swedish CABRERA display format aVR is displayed as mirror image (i.e., -aVR) between standard leads I and II. This CABRERA display in the frontal plane (aVL, I, -aVR, II, aVF, III) was supported by the 2007 Universal Definition of Myocardial Infarction document as offering more accurate spatial contiguity [1]. The 2002 ACC/AHA exercise testing guidelines also downplayed the value of aVR in interpreting exercise induced ischemia [2]. However, a recent collaborative international meta-analysis including 22,740 patients [3] found that aVR ST elevation independently predicted left main or 3-vesssel disease. The current article extends prior reviews [3,4] and also evaluates the impact of aVR ST changes on clinical outcome.

If one accepts aVR as facing the inside of left ventricular cavity and "reciprocal" to V_5 (positioned in the anterior axillary line) and V_6 (positioned in the mid axillary line), aVR should also be "reciprocal" to V_7 (positioned in the posterior axillary line). V_7 captured changes in the postero-apical part of the left ventricle but is not recorded on a standard 12-lead ECG. The reciprocal lead aVR will therefore contain unique information.

Comparing recordings on aVR with those on unipolar leads V_{5-7} referenced to the Wilson's Central Terminal (reflecting an iso-electric point inside the heart) is challenging, because the amplitudes of both QRS complex and ST deviation in V_{5-7} are dependent on the distance and nature of the conducting medium between the recording electrode and the epicardium [5,6]. As previously reviewed, lower amplitudes of ST changes are found in leads farther from the heart (V_{7-9}) than in the standard chest leads closer to the heart (V_{1-4}) during balloon coronary occlusion models [6]. Amplitude of ST changes from similar amount of ischemia varies among the chest leads and is lower for leads farther away.

With left ventricular sub-endocardial ischemia during stress test, ST depression may be observed in V_{5-7} and ST elevation in aVR. Not only is V_7 not routinely recorded, ST depression in leads $V_{5,6}$ may also be inconspicuous because of their longer distance from the heart, such as in patients with emphysema. A recent article [7] reported 454 stable patients in whom rest and stress ECG, clinical parameters, and single photon emission computed tomographic myocardial perfusion imaging (MPI) data were correlated with angiographic data—75 had left main or ostial left anterior descending (LAD) disease, 276 had coronary disease in other sites and 103 had no disease. While ST depression in inferolateral leads was always significant on univariate analysis to predict left main and ostial LAD disease, the predictive ability measured by the area under the curve (AUC) on logistic regression was much lower than aVR ST elevation. The AUC was 0.62 for V_4, 0.69 for V_5, 0.70 for V_6, 0.65 for II, 0.58 for III, 0.61 for aVF; and was 0.82 for aVR. On multivariate analysis, the strongest predictor was stress-induced ST elevation in lead aVR ($p<0.0001$), while left ventricular ejection fraction after stress and percent reversible LAD ischemia on MPI also contributed ($p<0.005$ and $p<0.05$ respectively). However, the univariate AUC was much lower at 0.60 and 0.64 respectively.

In the collaborative international meta-analysis [3], 4844 patients with stable angina underwent stress tests. Transient ischemic dilatation during stress test, ST elevation in aVR and V1 and hyperlipidemia were the most powerful predictors of left main or multi-vessel disease.

In the classical non-ST elevation acute coronary syndrome (ACS) the left ventricle is having subendocardial ischemia. Mechanistic explanation for aVR ST elevation is similar to stress induced ischemia. Table 1 reviews clinical outcomes in 4 recent studies [8–11]. A graded univariable relationship between aVR ST elevation and mortality is almost always observed. In the GRACE registry, aVR ST elevation did not add significantly to the GRACE score in prognostication [10]. However, the GRACE score contains age and creatinine, two strong prognosticators that do not indicate myocardial ischemia. Lead aVR ST elevation does and ischemia is potentially reversible with therapy. Using GRACE score to separate patients to low, medium and high risk, Tanglieri [11] reported that aVR ST elevation further stratified in-hospital mortality.

Because aVR is the only lead that faces directly the high inter-ventricular septum, an isolated transmural infarction there may not be diagnosed as STEMI because there is no lead contiguous to aVR [4].

* Department of Cardiology, Dunedin School of Medicine, University of Otago, Dunedin Hospital, Dunedin, New Zealand. Tel.: +64 3 4747980; fax: +64 3 4747655.
E-mail address: cheuk-kit.wong@healthotago.co.nz.