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Research Article

“The obesity paradox” in patients with atrial fibrillation according to the results of the REKUR-AF study

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Abstract

Introduction: to evaluate the effect of excess body weight (EBW) and obesity on the survival of patients with atrial fibrillation (AF) in the REKUR-AF study.

Materials and methods: A subanalysis of patients with AF included in the REKUR-AF (382 people) study was performed. Survival rates were analyzed in three patient groups: patients with normal body mass index (BMI), EBW and obesity. Then the nature and significance of the influence of the studied factor on the prognosis in patients with AF were assessed.

Results and discussion: Patients with AF and normal BMI were significantly older than those with obesity and EBW ($p<0.001$ and $p=0.021$, respectively). Among obese patients, hypertension was significantly ($p=0.0015$) more common (93.9%) compared to the group of patients with a normal BMI level (80.5%). The frequency of type 2 diabetes in obese patients prevailed over the same indicator in the groups of people with normal BMI and EBW ($p=0.007$ and $p=0.020$, respectively).

The analysis of the survival rate of patients with AF depending on the BMI level showed that this factor had a significant impact ($p=0.013$) on the prognosis. The group of individuals with a normal BMI level had a significantly lower survival rate than the cohort of patients with EBW ($p=0.011$) and OB ($p=0.025$). The final model for Cox regression analysis ($\chi^2=53.06$, $p<0.001$) included the following factors: age, form of AF, BMI, presence/absence of type 2 diabetes, presence/absence of previous hospitalizations, presence/absence of hypertension, and presence/absence of oral anticoagulant (OAC) intake.

Conclusion: The obtained results do not make it possible to unambiguously interpret obesity as a predictor of a positive outcome in this category of individuals.

Keywords

atrial fibrillation, factor, obesity, prognosis, survival.

Introduction

Atrial fibrillation (AF) is one of the most common tachyarrhythmia types nowadays. By the year 2030, the expected number of AF patients in Europe will reach 14–17 millions, with 120 000–250 000 new cases detected each year. The AF rate is about 3% among general adult population (20 years of age and older); frequency is higher among senior patients and people with associated conditions, such as arterial hypertension (AH), chronic heart failure (CHF), ischemic heart disease (IHD), heart valves failure, obesity, diabetes, and chronic kidney disease. AF progression usually depends on the general heart condition. For example, left ventricle hypertrophy and early vessel aging syndrome in patients with AH, left ventricle ejection fraction decrease below 40% in patients with CHF, history of myocardial infarction in IHD patients are considered as proven AF progression factors. AF is associated with a mortality increase, mostly related to strokes, heart failure or sudden cardiac death. Clinical guidelines on AF diagnostics and treatment show data on influence of some predictors on the survival rate and the circulation complications rate among AF patients: diabetes increases probability of embolic events, and AH is a significant stroke risk factor. AF patients with concomitant CHF are more likely to die independently of left ventricle ejection fraction. Patients with kidney failure have an increased risk of circulatory complications. It is proven that oral anticoagulant (OAC) intake has a positive impact on the prognosis in AF patients (All-Russian Scientific Society of Specialists in Clinical Electrophysiology; Arrhythmology and Cardiac Stimulation; Russian Society of Cardiology and Russian Association of Cardiovascular Surgeons 2017; Meshcherina et al. 2020; Ministry of Health of Russian Federation 2020; Hindricks et al. 2021).

Among non-cardiac predictors influencing AF occurrence, obesity plays an important role. Nevertheless there is no clear opinion on the influence of obesity on the outcome prognosis in AF patients. There is an ongoing discussion on the “obesity paradox” described in patients with AF along with AH and IHD. There are supporters and critics of the paradox, which is why additional research is needed to get a big picture of obesity impact on the prognosis of AF patients (Uretsky et al. 2007; Lavie et al. 2009; McAuley et al. 2012; Lavie et al. 2014; Druzhilov and Kuznetsova 2017; Lechi 2017; Druzhilov et al. 2018; Miklisanskaya et al. 2020; Proietti and Boriani 2020).

Aim of research: to evaluate the effect of overweight and obesity on the survival of patients with AF in the REKUR-AF study.

Material and methods

Research design

To reach the aim, a subanalysis of AF patients’ database included into REKUR-AF study was conducted, which was approved by The Regional Ethic Committee (Minutes of Ethic Committee Meeting of Kursk State Medical University #7 of 07.05.2015). The design and results of this study were published previously (Polshakova and Povetkin 2017, 2018, 2019).

Patients

To conduct the subanalysis, the data on the patients were collected (n=896), including the patients whose body mass index (BMI) could be calculated according to the medical documentation. Considering this criteria, the patients were divided into groups: 382 in general (192 malse and 190 females), out of them 301 were urban residents, and 81 received care from other medical facilities of Kursk region. The average patient age was 76 [60–76] years old. To calculate a survival rate, a monitoring was performed on when the patient reached the “final point” (outcome), which was death of any cause. Phone contacts with the patients or their relatives were used 9.0±0.55 months after creating the database. Maximum time of observation was 17 months; 37 patients reached the final point. The outcome pattern was the following: cardiovascular deaths – 62.2%, and other causes – 37.8%.

The formed patient cohort was divided into 3 groups depending on their BMI level. The first group – patients with normal BMI 18.5–24.9 kg/m^2; the second group – patients with excess body weight (EBW), BMI=25.0–29.9 kg/m^2; the third group – patients with obesity, BMI=30.0 kg/m^2 and more (Russian Society of Cardiology; Russian Scientific Medical Society of Physicians; Association of Clinical Pharmacologists 2017; World Health Organization). The groups were compared by the parameters related to the clinical status of the patients and by ways of pharmaceutical correction.

Statistic processing

The statistical data were processed by using the standard methods (Glantz 1999) and consisted of 2 stages. Firstly, there was a survival rate study of different BMI patients; secondly, an analysis of the impact of the researched factor on AF prognosis was completed. On the first stage, survival charts, single- and double Caplan-Mayer analysis were applied. The latter was used to study influence of medications – OAC prescription – on the patients’ survival rate depending on EBW or obesity presence. On the second stage, a Cox regression was used. As a data input method, the Backward stepwise approach was used, the predictor exclusion level being 0.05 (Sharashova et al. 2017a, 2017b).

To compare the impact of EBW and obesity as factors potentially influencing the prognosis in AF patients, when using a Cox regressive analysis, a comparison was made between different categories of clinical and pharmacological factors. The clinical category included: gender (female, male), age (under 60 y.o.; 60–75 y.o.; over 75 y.o.), AF type (paroxysm, persistent, constant), continuity of AF (less than 5 years; 5–10 years; more than 10 years), stable angina (no/yes), history of myocardial infarction (no/yes), class of CHF (≤class II; class III or class IV), glomerular filtration rate (GFR) (≥60; less than 60 ml/min/L,73 m^2), type 2 diabetes (no/yes), presence and grade of AH (no, 1, 2, 3) hospital admissions within one year before the research (no/yes), the CHA_2DS_2VASc score (≤2; 3–5; more than 5 points), and heart rate (HR) (≤70; 71–80; 81–90; more than 90 beats per minute). The pharmacological factors included using different medication types: OAC (no/yes), antiplatelet (no/yes), angiotensin-converting enzyme inhibitors (ACEI) (no/yes), angiotensin II receptor antagonists (ARA

II) (no/yes), beta-blockers (BB) (no/yes), Calcium channel blockers (no/yes), diuretics (no/yes), mineralocorticoid receptor antagonists (no/yes), antiarrhythmic drugs (no/yes), cardiac glycosides (CG) (no/yes), and statins (no/yes). The above factors were evaluated using the data obtained from analyzing the clinic charts of patients under study.

A model creation algorithm defined the most severe category of each factor (for example, age above 75, permanent AF, diabetes presence, 4th grade of CHF, previous hospital admissions) as a comparison criterion to evaluate the impact on the outcome. When conducting a Cox regression analysis, the basic parameters were the following: relative risk (RR) and 95% of the confidence interval (95% CI). The statistical significance of the indicators was evaluated by several criteria: Wilcoxon (Gehan) test when constructing life tables, a set of 3 indicators: Log rank, Breslow, Tarone-Ware – when conducting a Kaplan-Meier analysis, and a Wald criteria in Cox regression. The overall role of the factor was evaluated along with assessing the impact of individual categories (if there were more than 2 categories present).

Discrete values in four-section tables system were compared using the χ^2 criteria. The latter was evaluated with Yates'correction for continuity. The quantitative parameters were compared using Mann-Whitney or t-test (depending on values spread). With $p<0.05$ the result was considered as reliable. The results for absolute quantitative parameters, depending on the values spread, was shown in M±SD or Me [25–75 quartiles]; the relative indicators were shown in percentage.

Results and discussion

The comparison of the groups under study showed reliable differences on several indicators (Table 1). AF patients with normal BMI were significantly older than patients with obesity and EBW ($p<0.001$ and $p=0.021$, respectively). Among the patients with obesity, AH occurred significantly more ($p=0.0015$) frequent (93.9%), comparing to the patients with the normal BMI level (80.5%). It is associated with more ($p=0.043$) elevated level of diastolic blood pressure (DBP) in patients of the third group comparing to the first one. The type II diabetes rate in obese patients was elevated comparing to the same indicator in patient with normal BMI or EBW ($p=0.007$ and $p=0.020$, respectively). Patients with EBW had a more rare CHF rate ($p=0.036$) than obese patients. The comparison of the other parameter showed no significant difference.

The frequency of prescribing different medications in the studied groups was the same, except for a more significant ($p=0.019$) of ARA II usage in AF patients with obesity comparing to the patients with arrhythmia and normal BMI. The overall amount of renin-angiotensin-aldosterone system (ACEI+ARA II) inhibitors showed no significant difference in any of the groups. Moreover, more frequent ($p=0.014$) cardiac glycosides prescription was detected in the first group comparing to the second.

An additional analysis of the clinical and pharmacological factors was conducted for the AF patients with normal BMI and combined (EBW+obesity) group shows that significance of differences is maintained in the following indicators: age (75[64–80] and 66[60–75], respectively, $p<0.001$); AH occurrence rate (80.5% and 91.7%, respectively, $p=0.007$); DBP value (82.3±9.88 mm Hg. and 84.9±11.4 mm Hg, respectively, $p=0.049$); and diabetes rate (12.2% and 23.7%, respectively, $p=0.036$).

A survival analysis depending on a BMI level shows that this factor has a significant impact ($p=0.013$) on the prognosis (Table 2). Pairwise comparison of BMI categories stated that the patients with normal BMI had a clearly lower survival rate than patients with EBW (Wilcoxon criteria (Gehan)=6.506, $p=0.011$) and obesity (Wilcoxon criteria (Gehan)=5.016, $p=0.025$). The last two groups show no big difference on this parameter (Wilcoxon criteria (Gehan)=0.913, $p=0.339$).

Kaplan-Meier analysis, conducted with regard to this factor and its categories, confirms the data acquired when constructing life tables (Table 3).

Taking into account strategic influence of OAC prescription on stroke and system embolism events in AF patients, defining the outcome of the disease, a further analysis was conducted to compare the survival rate of patients with different BMI levels depending on whether they take OAC drugs. (Table 4). Significant impact of BMI on prognosis was detected in the AF patients not taking OAC. Pairwise comparison of BMI categories in this patient cohort shows a significant decrease in the survival rate among the patients with the normal BMI comparing to the patients with EBW (Wilcoxon (Gehan) criteria=5.558, $p=0.018$) and obesity (Wilcoxon criteria=5.362; $p=0.021$). The last two groups show no significant difference in this parameter (Wilcoxon (Gehan) criteria=0.498, $p=0.480$).

A regressive Cox analysis was conducted to evaluate the role of BMI and other factors influencing the AF patient prognosis. The final model ($\chi^2=53.06$, $p<0.001$), defining the priority factors with a significant impact on the outcome of AF patients included the following factors: age, AF type, BMI, presence of diabetes, presence of previous hospital admissions, AH presence, and OAC usage (Table 5).

Presence of the clinical factors listed above in non-severe AF patients led to a significant decrease in the negative outcome risks: age 60–75 – a 66.6% decrease in the risk of the lethal outcome comparing to the patients older than 75 years old. Paroxysmal or persistent AF comparing to constant AF reduced the chances of the negative prognosis almost by ¾ and $^4/_5$, respectively; obesity presence led to a 68.6% decrease in mortality from any cause comparing to the patients with normal BMI. No history of diabetes or previous hospital admissions led to a decrease in reaching "the final point" by AF patients by 73.7% and 91.1%, respectively. Presence of grade 2 and 3 AH was linked with a decrease in the negative outcome risk by almost $^4/_5$ and $^2/_3$, respectively, compared to the patients

Table 1. Comparison of Patients’ Characteristics

Parameters		Normal BMI (abs/%)	Excess body weight (abs/%)	Obesity (abs/%)	p		
		1	2	3	1–2	1–3	2–3
Total number of patients (n=382)		82/21.5	103/26.9	197/51.6	-	-	-
Gender	Male (n=192)	45/54.9	53/51.4	94/47.7	NA	NA	NA
	Female (n=190)	37/45.1	50/48.6	103/52.3	NA	NA	NA
BMI (kg/m^2)		23.51 [22.04–24.34]	27.68 [26.23–28.58]	34.42 [32.0–37.32]	<0.001	<0.001	<0.001
Average age (years old)		75[64–80]	68[61–77]	66[59–74]	0.021	<0.001	NA
AF continuity (years)		2.5[1–6]	4[2–6]	4[1–6]	NA	NA	NA
AF type	paroxysmal	17/20.73	13/12.62	NA	NA	NA	NA
	persistant	26/31.71	39/37.86	NA	NA	NA	NA
	permanent	39/47.56	51/49.52	NA	NA	NA	NA
BP and HR levels	SBP (mm Hg)	136.4±19.6	139.5±21.9	131.3±20.3	NA	NA	NA
	DBP (mm Hg)	82.3±9.88	84.4±12.4	85.2±11.0	NA	0.043	NA
	HR (bpm)	74[68–81]	70[64–80]	72[64–82]	NA	NA	NA
AH	Presence	66/80.5	90/87.4	185/93.9	NA	0.0015	NA
	Grade 1	7/10.61	12/13.33	25/13.51	NA	NA	NA
	Grade 2	21/31.82	20/22.22	50/27.03	NA	NA	NA
	Grade 3	38/57.57	58/64.45	110/59.46	NA	NA	NA
Stable angina	Presence	33/40.24	51/	97/49.24	NA	NA	NA
	Class I	0/	1/1.96	1/1.03	NA	NA	NA
	Class II	17/51.52	26/50.98	45/46.39	NA	NA	NA
	Class III	16/48.48	24/47.06	51/52.58	NA	NA	NA
Post-MI sclerosis	Presence	19/23.17	24/23.30	42/21.32	NA	NA	NA
CHF	Presence	81/98.78	95/92.23	193/97.97	NA	NA	0.036
	Class I	3/3.70	1/1.05	4/2.07	NA	NA	NA
	Class II	28/34.57	36/37.90	63/32.64	NA	NA	NA
	Class III	26/32.10	43/45.26	77/39.90	NA	NA	NA
	Class IV	24/29.63	15/15.79	49/25.39	NA	NA	NA
Type 2 diabetes	Presence	10/12.20	16/15.53	55/27.92	NA	0.007	0.020
GFR	Less than 60 ml/min/1.73 m^2	46/56.10	51/49.51	105/53.30	NA	NA	NA
Number of hospital admissions within the year before participation in study		1[1–1]	1[1–1]	1[1–1]	NA	NA	NA
CHA_2DS_2VASc	points	4[3–5]	4[3–5]	4[3–5]	NA	NA	NA
ACEI	Admission rate	63/76.83	74/71.84	137/69.54	NA	NA	NA
ARA II	Admission rate	5/6.10	14/13.59	35/17.77	NA	0.019	NA
MCRA	Admission rate	44/53.66	47/45.63	119/60.41	NA	NA	NA
Diuretics	Admission rate	55/67.07	69/66.99	137/69.54	NA	NA	NA
Antiplatelets	Admission rate	61/74.39	67/65.05	127/64.47	NA	NA	NA
BAB	Admission rate	47/57.32	69/66.99	134/68.02	NA	NA	NA
CCB	Admission rate	13/15.85	13/12.62	28/14.21	NA	NA	NA
AAD	Admission rate	31/37.80	27/26.21	66/33.50	NA	NA	NA
Statins	Admission rate	57/69.51	69/66.99	139/70.56	NA	NA	NA
CG	Admission rate	24/29.27	14/13.59	39/19.80	0.014	NA	NA
OAC	Admission rate	11/13.41	23/22.33	37/18.78	NA	NA	NA

Note: The percentage of the patients’ number in every group was calculated from the total number of patients. Percentage of the other parameters was calculated relatively to the number of patients in every group. AAD – antiarrhythmic drugs, ACEI – angiotensin converting enzyme inhibitor, AF – atrial fibrillation, AH – arterial hypertension, ARA II – angiotensin II receptor antagonists, BAB – beta-adrenal blockers, BMI – body mass index, BP – blood pressure, CCB – calcium canal blockers, CG – cardiac glycosides, CHF – chronic heart failure, DBP – diastolic blood pressure, GFR– glomerular filtration rate, HR – heart rate, MCRA – mineral corticoid receptor antagonists, MI – myocardial infarction, OAC – oral anticoagulants, SBP – systolic blood pressure.

without AH. No OAC usage led to an almost 4.6-time increase in the lethal outcome risk. Age under 60, EBW, grade 1 AH as the researched factor categories had positive but insignificant impact on AF prognosis.

Comparison of the AF patients with different BMI and included in REKUR-AF study shows a significantly elevated survival rate in the patients with obesity (91.4%) and EBW (94.2%) compared to the patients with normal BMI (82.9%). There is no significant difference between the results of the groups with obesity and EBW by this parameter. An analysis of the survival rates performed by Kaplan-Meier method yielded the same conclusion, which allows considering EBW and obesity as the factors leading to an increase in survival in AF patients under typical clinical observation within 9 months. Our results are in agreement with the literature sources data which detected presence of the “obesity paradox” in patients with cardiac diseases, including AF. A meta-analysis of the observational study of CHF patients, which included 28 209 people, A. Oreopoulous et al. (2008) showed that, comparing to normal BMI patients. CHF patients with EBW or obesity had lower rates of cardiovascular (19 and 40%, respectively) and general mortality (16 and 33%, respectively) within an average observation time of

Table 2. Comparison of Survival Rates in AF Patients With Different BMI Levels

Factor	Factor categories	Percentage of surviving patients	Wilcoxon (Gehan) criteria; p
	18.5–24.9	82.9%	
BMI	25.0–29.9	94.2%	8.678; p=0.013
	30 and more	91.4%	

Note: BMI – body mass index.

Table 3. Significance of Differences of Survival Parameters Evaluated by Kaplan-Meier Methods in AF Patients With Different BMI

Evaluation criteria	BMI	18.5–24.9 & 25.0–29.9	18.5–24.9 & 30 and more	25.0–29.9 & 30 and more
Long Rank	6.370; p=0.041	5.258; p=0.022	3.679; p=0.055	0.720; p=0.396
Breslow	8.617; p=0.013	6.491; p=0.011	4.986; p=0.026	0.910; p=0.340
Tarone-Ware	7.896; p=0.019	6.190; p=0.013	4.532; p=0.033	0.873; p=0.350

Note: this table shows χ^2 number and its statistical value; BMI – body mass index.

Table 4. Survival Rates Comparison in AF Patients With Different BMI Levels Taking and Not Taking OAC

Factor	Factor categories	Percentage of surviving patients		Wilcoxon (Gehan) criteria; p
		No OAC	With OAC	
	18.5–24.9	80.3%	94.6%	8.293; p=0.016 for No OAC
BMI	25.0–29.9	92.5%	100%	1.578; p=0.454
	30 and more	90.6%	100%	For With OAC

Note: BMI – body mass index, OAC – oral anticoagulants.

2.7 years. The "obesity paradox" in case of CHF was also discovered in a study of only BMI, fat tissue percentage, and abdominal size (Oreopoulos et al. 2008; McAuley et al. 2012; Lavie et al. 2014; Druzhilov et al. 2018). In the cases described in the above papers, the observation period lasted for several years.

In some published articles, a prognosis of AF patients with different BMI levels and OAC prescription was evaluated (Badheka et al. 2010; Sandhu et al. 2016; Proietti et al. 2017). Our analysis of the survival rate in AF patients with different BMI levels and OAC prescription has shown significant impact of BMI only in patients not taking OAC. This result is probably due to the fact that patient group taking OAC was small (n=71) and no lethal outcomes were registered among the patients with EBW or obesity.

Pairwise comparison of the survival rates among the patients not taking OAC and having different BMI levels showed a significant increase in the researched parameter between the patients with EBW or obesity and the normal BMI patients. The EBW and obesity groups showed no big difference.

It was important to compare BMI levels and other parameters potentially causing a negative outcome in AF patients. A regressive Cox analysis was carried out to evaluate a role of BMI and other factors influencing the

Table 5. Characteristics of Factors Included in AF Patients Risk Evaluation Model

Factor	RR	95% CI		p
		Bottom level	Top level	
Age				0.019
Age <60 y.o.	0.455	0.186	1.113	0.085
Age 60–75 y.o.	0.334	0.147	0.760	0.009
AF type				0.001
Paroxysmal AF	0.277	0.093	0.827	0.021
Persistent AF	0.156	0.062	0.392	0.001
BMI				0.045
EBW	0.490	0.225	1.069	0.073
Obesity	0.314	0.118	0.836	0.020
Without diabetes	0.263	0.117	0.588	0.001
Without hospital admissions	0.089	0.012	0.668	0.019
AH				0.032
1st grade	0.492	0.164	1.474	0.205
2nd grade	0.146	0.036	0.582	0.006
3rd grade	0.382	0.154	0.952	0.039
Without OAC	4.576	1.072	19.523	0.040

Note: AF – atrial fibrillation, AH – arterial hypertension, BMI – body mass index, EBW – excess body weight, OAC – oral anticoagulants.

prognosis in AF patient. Predictors having a positive impact on the prognosis included the following factors: age, AF type, BMI, presence of diabetes, presence of previous hospital admissions a year before a study, and presence of AH grades 2–3. Lack of OAC prescription leads to a significant increase in the death risk.

Considering all the listed above, presence of EBW and obesity can be considered as the factors improving the prognosis in AF patients. Nevertheless, our research yielded some data which prevent us from saying that excess BMI has a clearly positive impact on AF progression. Among the factors limiting the positive effect from EBW are the following: age factor, with the patients with normal BMI levels being significantly older than those with EBW or obesity; an increased diabetes rate, AH and elevated DBP levels in obese patients comparing to patients with normal BMI, and an increased CG usage in patients with normal BMI compared to the second group.

Among the listed factors, older age and more frequent CG intake among patients from the first group could worsen the prognosis. An increased rate of diabetes among obese patients is expected and understandable, but a small number of such patients and lack of blood glucose control among all the patients under study prevents from considering it as an AF progression predictor. An elevated AH rate is also expected in normal BMI patients group. Still that does not explain better survival rates in obese patients. There is a good level of hypotensive drug usage and relatable blood pressure control levels in the studied groups, excluding DBP in patients with normal BMI and obesity, which can be used as an argument.

There is a number of articles which doubt the existence of the "obesity paradox" in any patients, including those with cardiac and circulatory diseases (Habbu et al. 2006; Hu 2008; Druzhilov et al. 2018; Carbone et al. 2019; Stovitz 2019a, 2019b; Miklisanskaya et al. 2020; Proietti and Boriani 2020). It is, first of all, connected with some methodological failures found in different studies. It is impossible to include all predictors affecting the survival rate among patients with and without obesity, which is possibly the main factor causing doubts whether EBW and obesity could positively affect patients with AF and other cardiac pathologies.

Conclusion

A complex analysis of a number of clinical and pharmacological parameters in AF patients included in REKUR-AF study allowed concluding that there is a positive influence of EBW and obesity on the outcome prognosis. This is not an unambiguous conclusion: there are some factors included in the study that could negatively influence the survival rate in patients with normal BMI, such as older age or an elevated rate of some medicine intake (CG). Some evaluated predictors cannot be clearly analyzed due to insufficient data.

In conclusion, a subanalysis of REKUR-AF study on the "obesity paradox" in AF patients and comorbid diseases yields the unclear results that cannot make it possible to regard obesity as a positive predictor in these patients. Therefore, further expanded research is needed.

Research limitations

Nine months after the database creation (n=896), the information about the status of the patients included in the subanalysis was available in 42.6% of cases, which could have affected the final results. Some role in the research limitations could be played by a wide variety of the evaluated predictors of prognosis in AF patients with obesity.

Conflict of interest

All the authors deny any conflict of interests to disclose in this paper.

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