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The checkmark association between gamma glutamyl-transpeptidase and body mass index in a large Chinese population.

Wendan Mei[1], Yicheng Fang[1], Chenxu Wang[1], Xia Ren[1], Jian Hu[1], Fan Su[1], Grace Tavengana[1], Huan Wu[2], Yufeng Wen[1]

1 School of Public Health, Wannan Medical College, Wuhu, Anhui Province, China, 22 West Wenchang Road, Wuhu, Anhui Province 241002, China.
2 School of Laboratory Medicine, Wannan Medical College, Wuhu, Anhui Province, China, 22 West Wenchang Road, Wuhu, Anhui Province 241002, China.

Correspondence to: Yufeng Wen, doctorate
School of Public Health, Wannan Medical College, 22 West Wenchang Road, Wuhu, Anhui Province 241002, People Republic of China
E-MAIL: wyf2015w@sina.com

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Abstract

BACKGROUND: Obesity has long been regarded as a risk factor for abnormal liver function, although the quantitative relationship between them is not clear. This study aimed to investigate the relationship between body mass index (BMI) and gamma-glutamyl transpeptidase (GGT) in different gender populations.
METHODS: The cross-sectional study included 221,934 people aged over 18 years and under 90 years who underwent physical examinations at Yijishan Hospital in Wuhu City from 2011 to 2016. t-test and Chi-square test were used to compare the differences in demographic characteristics and biochemical indexes between men and women. Linear regression model and smooth curve method were used to investigate the relationship between BMI and GGT.
RESULTS: The smooth curve shows a checkmark association between GGT and BMI. After adjusting for confounders, the cut-off BMI for the whole population was 19.5 kg/m^2. When BMI was less than 19.5 kg/m^2, GGT levels decreased with increasing BMI, and when BMI was greater than 19.5 kg/m^2, GGT levels increased with increasing BMI. After gender stratification, there was a checkmark association between male and female GGT levels and BMI, but the trend of male GGT levels changing with BMI was more obvious than that of females.
CONCLUSIONS: Our investigation demonstrated that the GGT level in obese Chinese people is significantly higher than that in non-obese people living in Wuhu City. BMI level can be considered as an early warning index for diseases related to liver function injury in the clinic, although the influence of gender difference should be specifically considered.

ORIGINAL ARTICLE

Abbreviations:

BMI	- body mass index
GGT	- gamma-glutamyl transpeptidase
ALT	- alanine transaminase
AST	- aspartate aminotransferase
DBIL	- direct bilirubin
TBIL	- total bilirubin
SBP	- systolic blood pressure
DBP	- diastolic blood pressure

INTRODUCTION

The global prevalence of overweight and obesity has exceeded 50%(Blachier *et al.* 2013; Yu *et al.* 2012). Obesity, as a chronic disease, has become one of the most relevant public health threats (Sorrie *et al.* 2017). Obesity is linked to cardiovascular disease, but it is also a major cause of liver dysfunction and related diseases (Vimaleswaran *et al.* 2015). Therefore, it is critical to identify people at risk for obesity-related diseases as early as possible (De Lorenzo *et al.* 2019). Gamma-glutamyl transpeptidase (GGT) is an enzyme located on the outer membrane of the cells wich controls the metabolism of glutathione, the principal cellular antioxidant thiol (Mitrić *et al.* 2023), it mainly exists in liver cells and is secreted to the human digestive system (Yang *et al.* 2018). When human hepatocyte synthesis is hyperactive or bile excretion is blocked, serum GGT level will increase (Hoffmann & McKiernan 2017). Therefore, GGT is frequently considered a sensitive indicator of alcohol intake, fatty liver disease, and hepatitis (Lala *et al.* 2021). Different studies have shown that compared with other risk indicators, obesity has a strong correlation with GGT, rising gradually with the increase in obesity degree (Ali *et al.* 2021; Jalili *et al.* 2022). The increased trend in the average GGT level was associated with a higher prevalence of obesity in recent population surveys (Alatalo *et al.* 2008; Lee *et al.* 2006).

Clinical studies suggest that BMI is a good predictor of elevated hepatic enzymes and triglycerides in people from different world regions and a biomarker of hepatocellular toxicity. Although much evidence suggests that obesity may predict the GGT level (Kim & Han 2018; Chen *et al.* 2021; Boregowda *et al.* 2020), little is known about the effects of gender on the relationship. The reference range of the GGT level is significantly different by gender, being higher in men than in women(Kalirawna *et al.* 2021). Furthermore, GGT concentrations have been associated with all-cause and cause-specific mortality in Chinese adults with type 2 diabetes. However, the relationship of GGT with excessive body weight has been little explored among female and male Chinese patients. Therefore, this study was conducted to address the issue of the differential effects of BMI on the GGT level between genders in a large sample size clinical examination population.

METHODS AND PROCEDURES

Study population

This study was a cross-sectional study of 434,487 persons who underwent clinical evaluation in our hospital in East China from 2011 to 2016. The Medical Ethics Committee of Wannan Medical University approved the investigation and considered that the study only needed to obtain the oral informed consent of the participants. Therefore, every person provided oral informed consent. Furthermore, personal private information data was deleted when the results were analyzed. All studied people had physical examinations and blood biochemical studies. The researchers recorded the results of physical examinations and

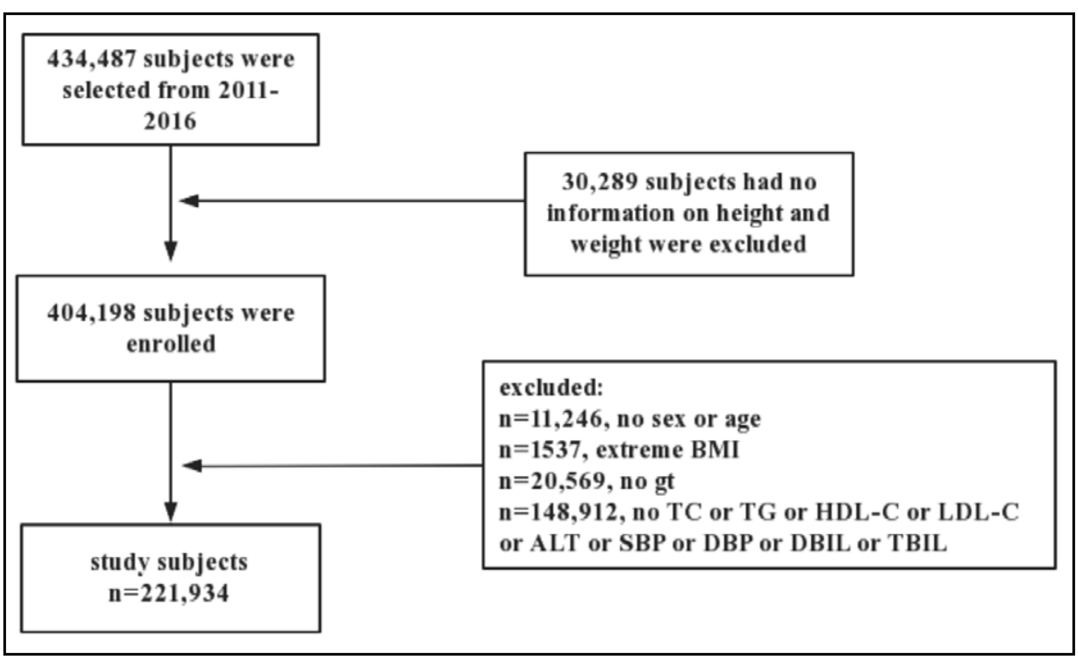

Fig. 1. Flow diagram of subjects included in the cross-study. ALT: Alanine transaminase; BMI: Body mass index; HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol; GGT: Gamma-glutamyl-transpeptidase; TC: total cholesterol; AST: Aspartate Transaminase, DBIL: direct bilirubin; TBIL: total bilirubin; SBP: systolic blood pressure; DBP: diastolic blood pressure;

Tab. 1. Comparison of demographic characteristics and biochemical indicators by genders

	Women (n = 98,271)	Men (n = 123,663)	t/χ^2	*p*
GGT (U/L)	18.16 ± 16.75	38.44 ± 31.26	-183.547	< 0.001
BMI (kg/m^2)	22.81 ± 3.12	24.54 ± 3.10	-129.786	< 0.000
Age (years)	47.28 ± 13.13	48.43±13.24	-20.582	< 0.001
ALT (U/L)	19.18 ± 15.51	32.30±26.02	-139.536	< 0.001
AST (U/L)	20.41±10.47	24.91±14.01	-83.803	< 0.001
DBIL (U/L)	3.64±1.79	4.40±2.17	-88.189	< 0.001
TBIL(U/L)	14.20±5.51	16.68±6.85	-92.325	< 0.001
Albuminumin(U/L)	47.13±3.24	48.41±3.29	-91.784	< 0.001
SBP (mmHg)	115.66±17.09	122.12±16.19	-90.002	< 0.001
DBP (mmHg)	74.30±9.29	79.70±9.78	-131.853	< 0.001
Drinking	1,389(1.41%)	70,036(56.63%)	76,504.464	< 0.001
Smoking	210(0.21%)	56,564(45.74%)	59,616.686	< 0.001

Notes. GGT Gamma-glutamyl transferase, BMI body mass index, ALT alanine Transaminase, AST aspartate aminotransferase, DBIL conjugative bilirubin, TBIL total bilirubin, SBP systolic blood pressure, DBP diastolic blood pressure

biochemical tests for all participants, such as age, sex, systolic and diastolic blood pressure, smoking, alcohol consumption, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBiL), bound bilirubin (DBIL), and albumin.

The exclusion criteria for the study were as follows (Figure 1): (1) people without height or weight measurement information; (2) Age under 18 years old or over 90 years old; (3) incomplete data or extreme values of gender, age, BMI, GGT, SBP. DBP and lipid parameters. In this study, 221,934 people who met the criteria were finally analyzed, 123,663 men accounting for 55.7% with an average age of 48.43±13.24 years old, and 98,271 women accounting for 44.3% with an average age of 47.28±13.13 years old.

This study was based on data from the Health Management Center at the First Affiliated Hospital of Wannan Medical College in Wuhu, China. Since the participants in this study came to the hospital for routine physical examinations, the Medical Ethics Committee of Wannan Medical College approved that the study only needs to obtain the participant's verbal informed consent. Therefore, the study did not obtain written informed consent from the subjects, but verbal consent was obtained from the participants. All methods in the current research were conducted by the Declaration of Helsinki guidelines and regulations.

Study variables, physical characteristics, and biochemical measurements

A questionnaire was used to collect relevant demographic and behavioral characteristics, medical history, and surgical history. Demographic and behavioral characteristics include age, gender, smoking, and alcohol consumption. The smoking behavior was defined as continuous or cumulative smoking for more than six months, smoking at least one cigarette a day and still smoking, otherwise defined as non-smoking; Drinking behavior was defined as consuming alcohol on more than four days a week, including more than 20 grams per session per day.

The people's general physical characteristics were first measured by professionals using standard methods to measure height, weight, blood pressure, and other variables following the World Health Organization Guidelines. Height measurement requires the subject to stand barefoot on the floor of an altimeter, with a naturally straight torso, straight head, eyes staring ahead, upper limbs naturally hanging down, and legs straight. The recorded height data is accurate to 0.1 cm. Weight measurement requires the subject to stand barefoot, wearing shorts, naturally in the center of the weighted pedal, keeping their body stable. The recorded data is accurate to 0.1 kg. BMI is calculated by dividing weight (kg) by the square of height (m), with an accuracy of 0.01 kg/m^2. Blood pressure measurements were performed with a mercury sphygmomanometer.

Fasting venous blood samples (5 mL) were collected in the morning, and the serum enzymological examination was conducted. ALT, AST, TBIL, DBIL, albumin, GGT, and other indexes of all samples were analyzed within 24 hours. The instrument for detecting GGT level was an Olympus AU-2700 automatic vividness analyzer.

Statistical methods

SPSS 26.0 software and R-project 4.2.1 were used for statistical analyses of the results. Continuous variables normally distributed are reported as means ± standard deviations. The *t*-test and *chi*-square test were

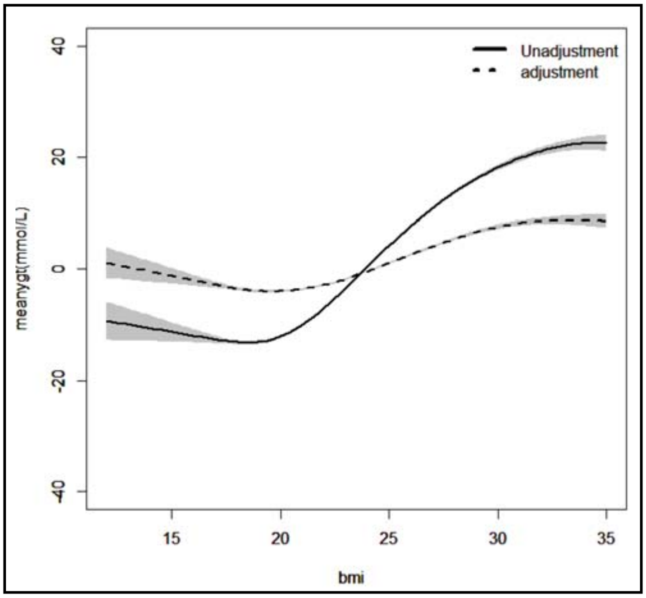

Fig. 2. Generalized smoothing splines for GGT and BMI. Horizontal coordinates represent different components, while vertical coordinates represent residuals of GGT. Solid line: no adjustment; dashed line: adjusted for age, gender, SBP, DBP, smoking, drinking, ALT, AST, TBIL, DBIL, and albumin. The shaded area shows the 95% confidence interval.

applied to compare the differences in demographic characteristics, physical examination indicators, and blood biochemical indicators between the male and the female. The relationship between BMI and GGT was tested by the generalized smooth spline, and the node position was automatically generated in the generalized additive model with R-packet MGCV. The adjusted factors were age, gender, SBP, DBP, smoking, drinking, ALT, AST, TBIL, DBIL, and albumin. According to the location of BMI nodes, the linear regression model was further used to analyze the relationship between BMI at different segments and GGT, and the influencing factors such as age, SBP, DBP, smoking, drinking, ALT, AST, TBIL, DBIL, and albumin were adjusted. All the p-values were double-tailed, and the significance level was 0.05.

RESULTS

General characteristics of studied participants

There were statistically significant differences in GGT, BMI, age, ALT, AST, DBIL, TBIL, albumin, systolic blood pressure, diastolic blood pressure, drinking and smoking habits between male and female groups (Table 1) ($p < 0.05$).

Relationship between BMI and GGT in the whole population

There was a checkmark association between GGT and BMI in the population (Figure 2). After adjusting for confounders, the cut-off BMI for the whole population was 19.5 kg/m^2. When BMI was less than 19.5 kg/m^2, GGT levels decreased with increasing BMI, and when BMI was greater than 19.5 kg/m^2, GGT levels increased with increasing BMI. Detailed results are shown in Table 2.

The relationship between body mass index by gender and GGT

Gender stratification analysis was performed on the study population. After adjusting for age, SBP, DBP, and other factors, the GGT level and BMI of both men and women showed a checkmark curve relationship, and the GGT level decreased first and then increased with the increase in BMI (Figure 3). The difference is that the trend of GGT level change is more obvious in men than in women, and the BMI cutoff values of the two groups are different. The BMI cut-off was 17.2 kg/m^2 for men and 18.9 kg/m^2 for women (Figure 3, Table 3).

DISCUSSION

This study demonstrated a checkmark association between GGT and BMI. After adjusting for confounders, the cut-off BMI for the whole population was 19.5 kg/m^2. When BMI was less than 19.5 kg/m^2, GGT levels decreased with increasing BMI, and when BMI was greater than 19.5 kg/m^2, GGT levels increased with increasing BMI. After gender stratification, there was a checkmark association between male and female GGT levels and BMI, but the trend of male GGT levels changing with BMI was more obvious than that of females. Especially in the overweight and obese population, the trend of increasing the GGT level with BMI in men is more obvious than that in women. These findings are consistent with previously reported results by some researchers that the average GGT level increased significantly with the increase in BMI (Reinehr *et al.* 2009). At the same time, the results of this study also

Tab. 2. Association between GGT and BMI by the linear regression model, adjusted for age, albumin, ALT, AST, drinking, DBP, DBIL, gender, SBP, smoking, and TBIL

BMI kg/m^2	Unadjusted				Adjusted			
	B	S.E	t	*p*	B	S.E	t	*p*
12 ≤ BMI ≤ 19.5	-0.304	0.110	-2.763	0.006	-0.484	0.098	-4.912	<0.001
19.5 < BMI ≤35	3.172	0.021	150.727	0.000	1.145	0.020	56.018	0.000

Notes. Adjusted for age, albumin, ALT, AST, drinking, DBP, DBIL, gender, SBP, smoking, and TBIL.

Tab. 3. Association between GGT and BMI by linear regression model in different groups, adjusted for age, albumin, ALT, AST, drinking, DBP, DBIL, gender, SBP, smoking, and TBIL

Gender	BMI (kg/m²)	Unadjusted				Adjusted			
		B	S.E	t	*p*	B	S.E	t	*p*
Men	12 ≤ BMI ≤ 17.2	-3.539	1.175	-3.011	0.003	-2.883	1.049	-2.747	0.006
	17.2 <BMI ≤35	3.077	0.028	108.579	0.000	1.553	0.028	54.543	< 0.001
Women	12 ≤ BMI ≤ 18.9	-0.300	0.116	-2.586	0.010	-0.301	0.105	-2.861	0.004
	18.9<BMI≤35	1.420	0.020	71.496	0.000	0.585	0.020	29.316	<0.001

Notes. Adjusted for age, albumin, ALT, AST, drinking, DBP, DBIL, gender, SBP, smoking, and TBIL.

found that the increase of human GGT level may be related to underweight (Choi *et al.* 2017).

The liver plays a crucial role in lipid metabolism. Lipids can accumulate in the liver due to the imbalance that exists between fat delivery to the liver from fat tissue storage or food intake and fat consumption as a component of lipoprotein (Goodman 2014). This partly explains why there is such a strong relationship between liver disease and obesity (Zhao *et al.* 2021). In general, being overweight or obese can lead to abnormal lipid metabolism, thus resulting in liver dysfunction (Liu *et al.* 2021). In people with elevated BMI, GGT levels also increased, and liver dysfunction increased with fat liver accumulation. People with higher BMI are more likely to suffer from fatty liver (Ghouri *et al.* 2010) which leads to an increase in the GGT level (Feng *et al.* 2020). It was reported that obesity was significantly positively correlated with liver function parameters, including AST, ALT, GGT, and ALP, and that participants with higher levels of visceral adipose tissue (≥113 cm²) had lower levels than those with higher levels of visceral adipose tissue (< 113 cm²) had poorer liver function (Verrijken *et al.* 2010).

Through gender stratification analysis the study found that in the total participants, the level of GGT in the male was generally higher than that in the female, and the changing trend with BMI was more significant than that in the male. The reference range of GGT level is generally 10-50 U/L for the male and 10-30 U/L for the female (Spoto *et al.* 2021). In addition, the higher levels of GGT in males may be because the smoking and drinking rates in males are significantly higher than those in females (Breitling *et al.* 2009). According to previous studies, both alcohol and tobacco consumption increase GGT levels in humans (Nivukoski *et al.* 2019; Lee *et al.* 2019; Chen *et al.* 2020; Jabbar &

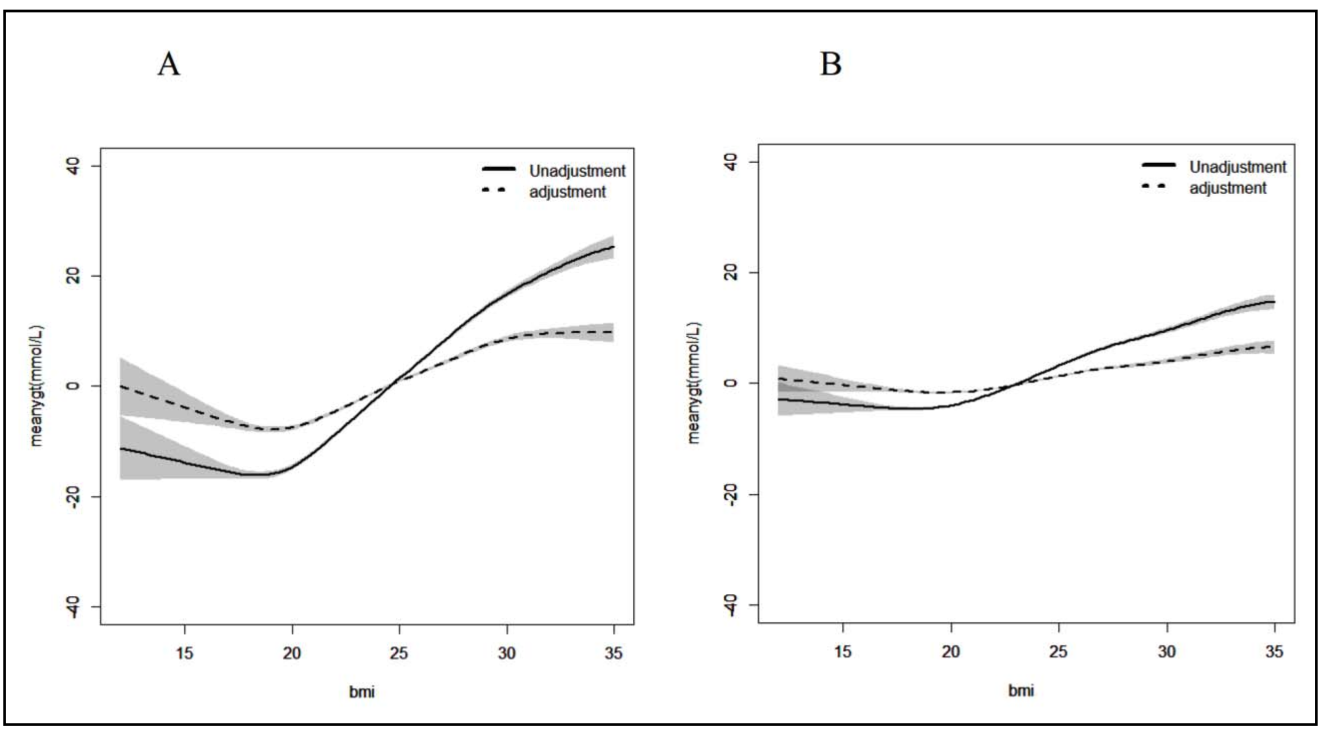

Fig. 3. Generalized smoothing splines for GGT and BMI in the male group (A), and the female group (B). Horizontal coordinates represent different components, while vertical coordinates represent residuals of GGT. Solid line: no adjustment; dashed line: adjusted for age, drinking, smoking, SBP, DBP, ALT, AST, TBIL, DBIL, and albumin. The shaded area shows the 95% confidence interval.

Abdul-Hassan 2017). In addition, the reason why the level of GGT in men with high BMI is higher than that in women may be because of the fat mass distribution: the majority of men have fat abdominal accumulation, while the majority of women are generally or gluteal-femoral obese (Stranges *et al.* 2004; Krotkiewski *et al.* 1983). The level of GGT in abdominal obesity is significantly higher than that in general obesity (Chang *et al.* 2013). In addition, several studies (Musso *et al.* 2010; Shannon & Abu-Ghannam 2019; Rusu *et al.* 2013; Bruwer 2014; Abdollahi *et al.* 2016; Polyzos *et al.* 2019) have found that various interventions, including lifestyle-related factors such as sustained weight loss (Shannon & Abu-Ghannam 2019), physical activity, and dietary factors (Rusu *et al.* 2013; Bruwer 2014; Abdollahi *et al.* 2016; Polyzos *et al.* 2019) significantly reduce circulatory GGT activity. Therefore, in daily life, we need to actively prevent related liver dysfunction caused by high BMI, and change lifestyle, such as quitting smoking, limiting alcohol consumption, and strengthening exercise, especially for male groups.

To sum up, Our investigation demonstrated that the GGT level in obese Chinese people is significantly higher than that in non-obese people living in Wuhu City, and the GGT levels in men are significantly higher than in women. BMI level can be considered as an early warning index for diseases related to liver function injury in the clinic, although the influence of gender difference should be specifically considered.

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COMPETING INTERESTS

The authors report there are no competing interests to declare.

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