BMJ Open

Lipid accumulation product and late-onset hypogonadism in middle-aged and elderly men: results from a cross-sectional study in China

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To cite: Sun K, Wang C, Lao G, *et al*. Lipid accumulation product and late-onset hypogonadism in middle-aged and elderly men: results from a cross-sectional study in China. *BMJ Open* 2020;**10**:e033991. doi:10.1136/bmjopen-2019-033991

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-033991).

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Received 03 September 2019
Revised 17 December 2019
Accepted 20 December 2019

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ABSTRACT

Objectives Hypogonadism in men is related to the deterioration of general health. However, the association between lipid overaccumulation and ageing-related hypogonadism remains an undetermined concept. We aimed to provide an insight into the possible links between the lipid accumulation product (LAP) and late-onset hypogonadism (LOH).

Setting Sun Yat-sen Memorial Hospital of Sun Yat-sen University.

Participants We included a population sample of 997 subjects aged 40 years or older.

Primary and secondary outcome measures The LAP was calculated by gender-specific equations using waist circumference (WC) and triglyceride (TG). LOH was defined by the presence of androgen deficiency symptoms and low serum total testosterone levels.

Results The prevalence of LOH was 9.4% in this population and gradually increased according to increasing LAP quartiles. Compared with subjects without LOH, ageing men with LOH had higher body mass index, WC, systolic blood pressure, percentage of subjects currently smoking, TG and follicle stimulating hormone and lower low-density lipoprotein cholesterol and sex hormone binding globulin. In multivariate logistic regression analysis, the adjusted ORs of LOH for increasing LAP quartiles 1–4 were 1.00 (reference), 1.10 (95% CI 0.45–2.69), 2.15 (95% CI 0.93–4.94) and 3.83 (95% CI 1.73–8.45), respectively.

Conclusion Body lipid accumulation evaluated by the LAP is independently associated with the prevalence of LOH in middle-aged and elderly Chinese men.

Strengths and limitations of this study

- The results of this study will provide an insight into the body lipid accumulation in the management of hypogonadism.
- Androgen deficiency is assessed with both total testosterone levels and related symptoms from the international index of erectile function-5 questionnaire.
- Results of the current study should be interpreted cautiously due to the observational design.
- Some important hormones, such as thyroxine, growth hormone and cortisol, should be considered to evaluate to strength the present findings.
- External studies are necessary to verify our findings in other ethnic groups.

INTRODUCTION

Late-onset hypogonadism (LOH) is associated with advancing age and is characterised by symptoms of androgen deficiency and low serum testosterone.[1] Hypogonadism with clinical symptoms can lead to decline in exercise tolerance and muscle mass and an attenuation of bone strength, which may significantly reduce quality of life.[2] Moreover, the clinical consequences of testosterone deficiency are associated with hypertension and many other cardiovascular risk factors. Previous prospective studies have shown that a decrease in serum testosterone was associated with mortality from cardiovascular disease and from all causes in older men.[3–5] Therefore, it is crucial and urgent for the early screening of LOH in the ageing population.

To date, epidemiological data seem to find a bidirectional relationship between the distribution of adipose tissue and hypogonadism. In a recent meta-analysis, Corona *et al* found that body weight loss is associated with a consistent increase in testosterone levels.[6] In turn, it is well documented that testosterone may have potential benefits on adipose tissue distribution, as androgen replacement treatment has been shown to increase muscle mass.[7] However, the increase in adipose tissue deposition may interact with hypogonadism, which is often overlooked in clinical practice.

Clearly, the degree of correlation between obesity and hypogonadism is complicated. For the purpose of evaluating the complex association of obesity with hypogonadism, exploring a simple and accurate method for the assessment of adipose tissue distribution

could be the first step. The lipid accumulation product (LAP) is a developed index of visceral lipid overaccumulation that can be used for evaluating cardiometabolic risk factors in adults.[8] Compared with other traditional anthropometric indicators, the LAP is found to be a reliable predictor for the evaluation of metabolic profiles and cardiovascular risks in a healthy population.[9–11] As described in our previous study, compared with other body adiposity measures, we found that the LAP could be a better parameter in the evaluation of the association between lipid accumulation and diabetes.[12] However, studies regarding the application of the LAP to ageing men and the correlation between the LAP and LOH are very limited. We analysed data from a community-based group to comprehensively look into the possible association between the LAP and LOH.

METHODS

Study population

A cross-sectional study was conducted in a community from June to November 2011 in Guangzhou, China. We originally planned to recruit 1000 middle-aged and elderly Chinese men from the cohort of the Risk Evaluation of cAncers in Chinese diabeTic Individuals: A lONgitudinal (REACTION) study. The details of the baseline survey and the study population of the REACTION study have been previously reported.[13–15] Briefly, we recruited 1002 male subjects who signed the consent form and agreed to undergo assessments of male sexual function in the present survey. Subjects who failed to provide information (waist circumference (WC): n=1; triglyceride (TG): n=3; International Index of Erectile Function-5 (IIEF-5): n=1) were excluded. Accordingly, 997 individuals were included in the final data analyses. The details of the selection of study participants are presented in a flow diagram (figure 1).

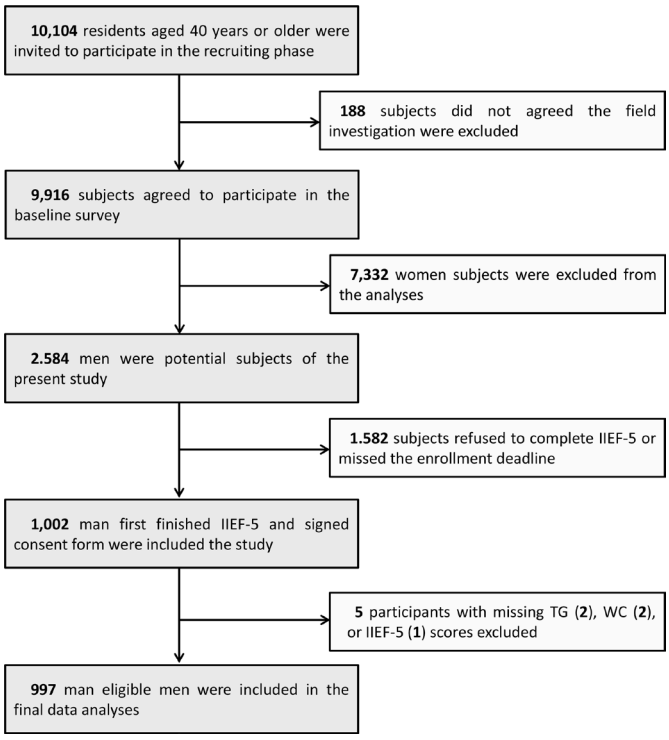

Figure 1 Flowchart of the selection of the study participants. IIEF-5, the International Index of Erectile Function-5; TG, triglyceride; WC, waist circumference.

Clinical and biochemical measurements

We used a standardised questionnaire to collect information on lifestyle factors, family history, sociodemographic characteristics and symptoms of androgen deficiency. Smoking and drinking habits were classified as 'never', 'current' (smoking or drinking regularly in the recent half year) or 'ever' (the cessation of smoking or drinking for more than half a year).[16] Anthropometrical measurements with standard protocols were carried out by trained staff. The average of three measurements of blood pressure was used for analysis, and hypertension was estimated using the Seventh Report of the Joint National Committee recommendations.[17] Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Obesity was defined as a BMI equal to or greater than 28, and overweight was defined as a BMI greater than or equal to 24 and less than 28.[18] WC was measured in all participants at the umbilical level in the standing position. Central obesity was defined as a WC greater than or equal to 90 cm.

After at least 8 hours of overnight fasting, venous blood samples were collected and centrifuged at 25°C and stored at −80°C until use for laboratory tests. Because of the possible circadian variation of testosterone and other hormones, we collected individual blood samples between 7:00 am and 9:00 am in the morning. The measurement of TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting plasma glucose (FPG) was performed using an auto-analyser (ARCHITECT ci16200 Integrated System, Abbott Laboratories, USA). Total testosterone (TT), luteinising hormone (LH) and follicle stimulating hormone (FSH) were determined by chemical immunofluorescent techniques (IMMULITE 2000 Immunoassay System, Siemens Healthcare Diagnostics, USA). Sex hormone binding globulin (SHBG) was measured by ELISA (DRG International, USA). The intra-assay and inter-assay coefficients of variation were 4.7%–7.5% and 2.5%–3.3%, respectively, for the evaluation of TT. Free testosterone (FT) was calculated with the Vermeulen formula and with the measurements of TT, SHBG and albumin.[19 20] Diabetes was diagnosed according to the 1999 WHO diagnostic criteria.[21]

Definition of LOH and body adiposity measurements for the calculation of the LAP

We applied the IIEF-5 questionnaire, which is the sum of the ordinal responses to questions related to the sexual problem of erectile dysfunction over the past 6 months, for the evaluation of symptoms of hypogonadism.[22] There are five categorisations of hypogonadism based on IIEF-5

scores (22–25: no hypogonadism; 17–21: mild; 12–16: mild to moderate; 8–11: moderate; 5–7: severe). The diagnosis of LOH was based on the combination of the symptoms of androgen deficiency (IIEF-5≤21) and low serum TT levels (<11 nmol/L) in the present study.[20 23] The LAP was calculated by gender-specific equations and calculated using the following formulas in male subjects: (WC−65)×TG.[8]

Statistical analysis

In the data analyses, continuous variables were presented as the means±SD except for skewed variables, which were presented as medians (interquartile ranges). Categorical variables were expressed as numbers (proportions). LAP was presented as quartiles, and linear regression analysis was used to test for trends across groups. Differences among groups were tested by one-way ANOVA, and post hoc comparisons were performed using Bonferroni correction. Comparisons between categorical variables were performed with the χ^2 test. Unadjusted and multivariate-adjusted logistic regression analysis were used to assess the prevalence of LOH in relation to each quartile increase in LAP level. Model 1 is unadjusted. Model 2 is adjusted for age. Model 3 is adjusted for age, LH and SHBG. Model 4 is adjusted for age, LH, SHBG, current smoking status and current drinking status. ORs and the corresponding 95% CIs were calculated. The association of LAP level with prevalent LOH was also explored in subgroup analyses and stratified by age (40–50, 50–60, 60–70 and >70 years), BMI (normal/overweight/obesity), central obesity (yes/no), diabetes (yes/no) and hypertension (yes/no). Interactions were tested by including strata factors, the quartiles of LAP level and the respective interaction terms (strata factors multiplied by quartiles of LAP level) simultaneously in the models.

Statistical analysis was performed using SAS V.9.3 (SAS Institute). All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

Characteristics of the participants

The mean age was 60.1±7.6 years among the 997 enrolled subjects, and the prevalence of LOH was 9.4% in the present study. The general features of subjects with LOH are shown in table 1. Ageing men with LOH had significantly higher BMI, WC, systolic blood pressure (SBP), TG, FSH, prevalent dyslipidaemia and prevalent hypertension and lower LDL-C, IIEF-5, TT, SHBG, FT and percentage of currently smoking than those without LOH (all p<0.05). As shown in table 2, the clinical and biochemical characteristics of the participants were divided into four groups according to LAP quartiles. Subjects in higher LAP quartiles had higher BMI, WC, SBP, diastolic blood pressure (DBP), TG, FPG, prevalent dyslipidaemia and prevalent hypertension and lower HDL-C, TT, LH, FSH and SHBG in the study than subjects in lower LAP quartiles (all p for trend <0.05).

Associations of the LAP with prevalent LOH

As shown in figure 2, the prevalence of LOH according to LAP quartile was 4.3, 5.3, 10.0% and 18.4%, respectively, for quartiles 1–4 (p for trend <0.0001). Compared with subjects in LAP quartile 1, univariate logistic regression analysis showed that those in quartile 2, quartile 3 and quartile 4 had significantly increased odds of prevalent LOH (table 3, p for trend <0.0001). The stability of the findings was verified in multivariate-adjusted logistic regression analyses. In model 4, after adjusting for age, LH, SHBG, current smoking status and current drinking status, the ORs of LOH for increasing LAP quartiles 1–4 were 1.00 (reference), 1.10 (95% CI 0.45–2.69), 2.15 (95% CI 0.93–4.94) and 3.83 (95% CI 1.73–8.45), respectively. Each one-quartile increase in the LAP was also associated with a higher prevalence of LOH in univariate (ORs 1.83, 95% CI 1.48–2.27) and multivariate-adjusted logistic regression analyses (ORs 1.67, 95% CI 1.32–2.12). The multivariate-adjusted ORs of elevated LAP quartiles with prevalent LOH in different subgroups are shown in figure 3. In subgroup analyses, the relationships of LAP level with prevalent LOH were not consistent. No statistically significant interaction term between quartiles of the LAP and each strata factor was detected in the subgroup analysis. We then analysed the associations of BMI and the prevalence of LOH to verify the performance of the LAP (online supplementary figure 1, online supplementary tables 1 and 2). In model 4 of the logistic regression analysis, the ORs of LOH for increasing BMI quartiles 1–4 were 1.00 (reference), 0.70 (95% CI 0.28–1.74), 1.65 (95% CI 0.74–3.66) and 3.28 (95% CI 1.55–6.92), respectively.

DISCUSSION

Evidence regarding the relationship between adiposity distribution measures and age-related pathological hypogonadism remains undetermined. The findings of the present study revealed a significant association of LAP levels with prevalent LOH in middle-aged and elderly Chinese men. The management of body lipid accumulation and fat distribution may have potential health benefits for hypogonadism therapy.

LOH is characterised by particular symptoms associated with decreased testosterone levels. We should note that some of the LOH subjects in the study may have had secondary hypogonadism, that is, below-normal TT levels but normal or low LH and FSH concentrations. Therefore, MRI should be performed for these subjects to exclude other evidence of pituitary or hypothalamic disease. With regard to deteriorated metabolic profiles in ageing men, Rotter *et al*[24] indicated that the LAP was negatively associated with TT and SHBG in 313 men aged 50–75 years old, emphasising that the LAP is applicable in the evaluation of age-related testosterone deficiency. However, their study did not assess the symptoms of androgen insufficiency by standardised questionnaire. The IIEF score is the most frequently used assessment

Table 1 Characteristics of study population by LOH status

	Without LOH	With LOH	P value
n (%)	903 (90.6)	94 (9.4)	<0.0001
Age (years)	59.8±7.5	62.1±7.7	0.0055
BMI (kg/m^{2*})	23.6±3.1	26.1±3.3	<0.0001
WC (cm)	86.2±8.9	92.9±9.3	<0.0001
SBP (mm Hg)	132.6±18.7	139.1±19.2	0.0014
DBP (mm Hg)	77.3±10.7	79.0±10.2	0.159
Current smoking (n (%))	288 (35.3)	19 (21.8)	0.0079
Current drinking (n (%))	87 (10.8)	8 (9.1)	0.2506
TG (mmol/L)	1.31 (0.98–1.80)	1.60 (1.14–2.65)	<0.0001
HDL-C (mmol/L)	1.20±0.28	1.09±0.22	0.1594
LDL-C (mmol/L)	3.37±0.95	3.10±0.96	0.0088
FPG (mmol/L)	5.92±1.63	6.21±1.66	0.1042
IIEF-5	17 (12–22)	13 (7–18)	<0.0001
TT (nmol/L)	19.16±5.76	9.02±2.28	<0.0001
LH (mIU/L)	5.55 (2.99–7.75)	5.16 (3.59–7.88)	0.8489
FSH (mIU/L)	10.42 (7.35–15.34)	10.86 (7.51–16.86)	0.0390
SHBG (nmol/L)	47.7 (30.2–85.8)	29.5 (18.8–47.4)	<0.0001
FT (pg/mL)	15.7 (12.5–18.5)	11.7 (6.3–14.8)	<0.0001
Dyslipidaemia (n (%))	103 (11.53)	19 (20.43)	0.0132
Hypertension (n (%))	178 (19.91)	27 (29.03)	0.0390
Diabetes (n (%))	89 (9.86)	13 (13.98)	0.2118

Data were means±SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.
P values were for the ANOVA or χ^2 analyses across the groups.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSH, follicle stimulating hormone; FT, free testosterone; HDL-C, high-density lipoprotein cholesterol; IIEF-5, the International Index of Erectile Function-5; LDL-C, low-density lipoprotein cholesterol; LH, luteinising hormone; LOH, late-onset hypogonadism; SBP, systolic blood pressure; SHBG, sex hormone binding globulin; TG, triglyceride; TT, total testosterone; WC, waist circumference.

questionnaire to evaluate sexual dysfunction in men and has been verified to have good performance in the assessment of the presence and severity of erectile dysfunction.[22 25] The IIEF score included 15 items in the original version. To improve the clinical applicability of the IIEF, a simplified 5-item version (IIEF-5) was developed.[26 27] To better estimate the relationship between the LAP and the clinical presence of LOH, we adopted the IIEF-5 score to assess the symptoms and signs of testosterone deficiency in the present study.

Our recent findings indicated that the LAP is a better indicator than other adiposity parameters in the assessment of visceral adiposity distribution, which should be given more consideration in clinical practice.[12] LOH is characterised as a particular clinical state with advancing age and is usually diagnosed on the basis of symptoms of androgen deficiency and a low level of serum testosterone. In this current study, it seems that the measurement of the LAP could be used to evaluate the association of lipid overaccumulation and LOH in ageing men. However, it remains unclarified how the LAP could provide a determination of deteriorated sexual function. As a continuous variable, the LAP is calculated based on a standard lipid profile (TG) and an anthropometric factor (WC).[8] Dyslipidaemia is a condition commonly found in men with hypogonadism. An evaluation of lipid profiles in participants who seek medical treatment for sexual dysfunction is therefore recommended in most guidelines on male sexual dysfunction.[28 29] A recent study by Corona *et al*[30] showed that hypertriglyceridemia is associated with significantly impaired penile blood flow and arteriogenic erectile dysfunction. Increased serum TG levels are related to decreased NO activity and production, which could promote endothelial dysfunction and accelerate atherosclerosis.[31]

Obesity is one of the common causes of reduced androgen in ageing men with hypogonadism.[20 32] While it is clear that the measurement of WC is reliable in the evaluation of visceral fat distribution, other underlying pathogenesis factors of LAP-associated LOH could be the secreted adipocytokines and inflammatory factors from visceral fat mass.[33 34] As an adipose hormone, leptin has been known to play a permissive metabolic role in the regulation of the hypothalamic–pituitary–gonadal axis.[35]

Table 2 Characteristics of study population by LAP quartiles

	Quartile 1 (−28.9 to 17.1)	Quartile 2 (17.2–29.1)	Quartile 3 (29.2–46.9)	Quartile 4 (47.0–488.0)	P for trend
Age (years)	60.6±7.5	60.6±7.3	59.5±7.6	59.4±7.8	0.0236
BMI (kg/m^2)	21.0±2.9	23.3±2.2*†	24.9±2.3*‡	26.3±2.9*‡†	<0.0001
WC (cm)	76.7±6.5	85.5±5.1*†	90.6±6.2*‡	94.4±7.3*‡†	<0.0001
SBP (mm Hg)	127.1±18.8	133.9±19.1*	135.0±17.6*	137.0±18.5*	0.0322
DBP (mm Hg)	73.9±11.0	77.8±9.6*	78.2±10.4*	80.0±10.9*	<0.0001
Current smoking (n (%))	77 (33.6)	60 (26.1)	79 (36.9)	91 (39.4)	0.0388
Current drinking (n (%))	19 (8.4)	27 (11.8)	23 (10.7)	26 (11.5)	0.5964
TG (mmol/L)	0.87 (0.71–1.09)	1.13 (0.96–1.36)*†	1.47 (1.24–1.75)*‡†	2.35 (1.86–3.20)*‡†	<0.0001
HDL-C (mmol/L)	1.34±0.28	1.22±0.28*	1.12±0.25*	1.07±0.21*	<0.0001
LDL-C (mmol/L)	3.17±0.86	3.39±0.82	3.54±0.93*	3.29±1.15†	0.0648
FPG (mmol/L)	5.7±1.4	5.9±1.4	6.0±2.1	6.1±1.6*	0.0030
IIEF-5	16 (10–21)	17 (13–21)*	17 (13–21)	16 (11–21)	0.2213
TT (nmol/L)	21.6±6.8	18.3±5.6*	17.0±5.8*	15.9±5.3*‡	<0.0001
LH (mIU/L)	6.30 (4.45–8.92)	5.29 (3.95–8.00)*	5.40 (3.70–7.69)*	5.13 (3.61–6.96)*	<0.0001
FSH (mIU/L)	12.02 (7.76–16.53)	10.61 (7.20–14.83)	10.27 (7.61–14.19)*	9.65 (6.64–14.03)*	0.0002
SHBG (nmol/L)	70.0 (40.8–145.0)	45.2 (28.8–74.4)*	41.9 (28.8–63.9)*	36.6 (23.5–59.5)*‡	<0.0001
FT (pg/mL)	15.8 (12.5–18.2)	15.1 (11.4–18.4)	15.4 (12.6–18.5)	14.6 (10.8–18.5)	0.2938
Dyslipidaemia (n (%))	13 (5.31)	20 (8.03)	38 (15.57)	51 (20.56)	<0.0001
Hypertension (n (%))	34 (13.71)	45 (18.22)	60 (24.49)	66 (26.72)	<0.0001
Diabetes (n (%))	23 (9.24)	25 (9.92)	30 (12.20)	24 (9.64)	0.6872

Data were means±SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.
P for trend was calculated for the linear regression analysis tests across the groups. P values were for the ANOVA or χ^2 analyses across the groups.
*P<0.05 compared with quartile 1 of LAP.
†P<0.05 compared with quartile 3 of LAP.
‡P<0.05 compared with quartile 2 of LAP.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSH, follicle stimulating hormone; FT, free testosterone; HDL-C, high-density lipoprotein cholesterol; IIEF-5, the International Index of Erectile Function-5; LAP, lipid accumulation product; LDL-C, low-density lipoprotein cholesterol; LH, luteinising hormone; SBP, systolic blood pressure; SHBG, sex hormone binding globulin; TG, triglyceride; TT, total testosterone; WC, waist circumference.

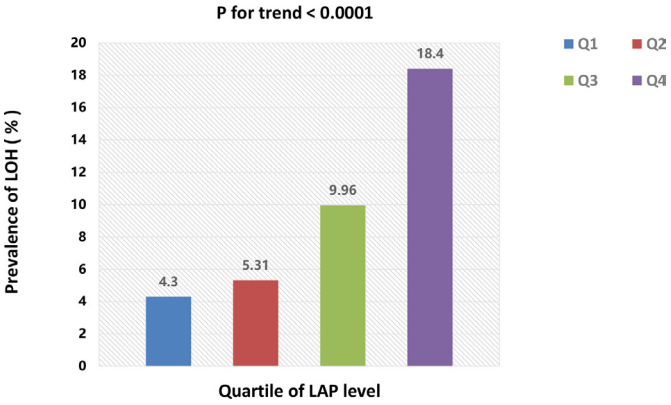

Figure 2 Prevalence of LOH in different LAP quartiles (Q1: −28.9 to 17.1; Q2: 17.2–29.1; Q3: 29.2–46.9; Q4: 47.0–488.0). LAP, lipid accumulation product; LOH, late-onset hypogonadism.

Increased fat mass is associated with elevated serum leptin levels, which in fact reflect leptin resistance and are responsible for the highly prevalent hypogonadism seen in obesity.[36] Inflammatory factors, including tumour necrosis factor-α, interleukin 1β and C reactive protein, are known to increase in subjects with obesity.[37–39] Based on previous findings, these inflammatory mediators also contribute to the suppression of the hypothalamic–pituitary–gonadal axis and the development of hypogonadism in obese men.

Certain limitations should be considered. First, due to the cross-sectional design of the study, no causal inference can be drawn. Further prospective cohort studies are required to determine the conclusive association between the LAP and the incidence of LOH. Second, recent clinical guidelines recommend the confirmation of a diagnosis of hypogonadism by repeating the measurement of

Table 3 The risk of prevalent LOH according to quartiles of LAP

LOH	Quartile 1 (–28.9 to 17.1)	Quartile 2 (17.2–29.1)	Quartile 3 (29.2–46.9)	Quartile 4 (47.0–488.0)	One quartile increase of LAP
Model 1	1	1.69 (0.73–3.93)	3.00 (1.37–6.57)	5.88 (2.81–12.32)	1.83 (1.48–2.27)
Model 2	1	1.69 (0.73–3.95)	3.18 (1.45–6.99)	6.37 (3.01–13.32)	1.88 (1.51–2.34)
Model 3	1	1.22 (0.51–2.91)	2.24 (0.99–5.04)	4.22 (1.94–9.18)	1.71 (1.36–2.16)
Model 4	1	1.10 (0.45–2.69)	2.15 (0.93–4.94)	3.83 (1.73–8.45)	1.67 (1.32–2.12)

Data are ORs (95% CI). Participants without LOH are defined as 0 and with LOH as 1.
Model 1 is unadjusted.
Model 2 is adjusted for age.
Model 3 is adjusted for age, LH and SHBG.
Model 4 is adjusted for age, LH, SHBG, current smoking status and current drinking status.
LAP, lipid accumulation product; LH, luteinising hormone; LOH, late-onset hypogonadism; SHBG, sex hormone binding globulin.

TT concentrations.[40] However, we evaluated testosterone deficiency on the basis of a single testosterone measurement in the present study. A comprehensive repeated assessment of TT concentrations is required to strengthen the findings of the present study, especially in those with obviously low testosterone levels. Third, it should be acknowledged that the study consisted only of Chinese subjects; thus, the present findings could not be fully extrapolated to subjects in other ethnic groups. Fourth, we assessed only the gonadotropin and TT in the present study; other important hormones, such as thyroxine, growth hormone and cortisol, should also be considered to strengthen the findings of the present study. Moreover, medications for relevant diseases, such as diabetes, hypogonadism, hypertension and dyslipidaemia, may influence the estimate of LOH. The absence of these data may influence risk estimates and result interpretation in this setting. Fifth, by including only Chinese subjects in the present study, the findings might not be applicable to individuals of other ethnicities, especially those in the developed or undeveloped countries.

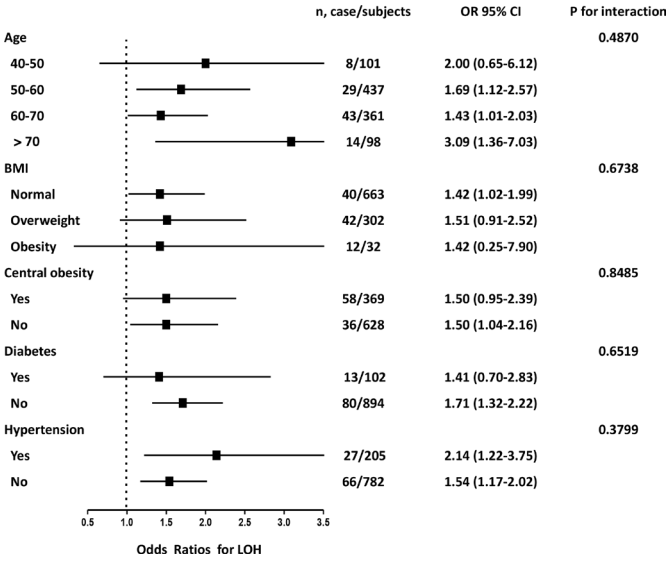

Figure 3 Prevalence of LOH with each quartile increase of LAP in different subgroups (BMI: normal <24; overweight 24–27.9; obesity ≥28). BMI, body mass index; LAP, lipid accumulation product; LOH, late-onset hypogonadism.

CONCLUSION

On the basis of data from nearly 1000 middle-aged and elderly Chinese participants, our study indicated that the adiposity distribution measure, the LAP, is independently associated with the prevalence of LOH. The findings of the present study suggested that we should pay more attention to symptoms of testosterone deficiency in ageing men with dyslipidaemia and adipose accumulation. Further external studies with a prospective design are necessary to verify our findings in different ethnic populations.

Acknowledgements We are indebted to the participants in the present study for their persistent outstanding support and to our colleagues working for their valuable assistance.

Contributors Conceived and designed the experiments: LY, FL and KS; performed the experiments: GL, DL, CH, KS, NL, LL and HX; analysed the data: KS and CW and wrote the manuscript: KS and HX.

Funding This work was supported by grants from: 1. The National Natural Science Foundation of China (81970696, 81600642, 81471034, 8137091, 81300675); 2. Natural Science Foundation of Guangdong Province, China (2015A030310433, 2017A030313831); 3. Sun Yat - Sen University Medical 2016 Youth Teacher Research Funding Project (16ykpy27); 4. Sun Yat-Sen Clinical Research Cultivating Program (SYS-Q-201801); 5. Major project of the people's livelihood science and technology in Guangzhou (201300000102); 6. The 863 project of Young Scientist (SS2015AA020927); 7. The Zhu jiang Star of science and technology Foundation in Guang Zhou (2014J2200046); 8. Grants from the Chinese Society of Endocrinology and National Clinical Research Center for Metabolic Diseases ; 9. State Key Clinical Specialty Construction Project (2011); 10. Science and Technology Planning Project of Guangdong Province, China (2014A020212161); 11. National Key R & D Program of China (No. 2016YFC0901200); 12. Sun Yat-sen University Clinical Research 5010 Program (2018021); 13. Yat-Sen Sailing Youth Fund (YXQH201916). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Institutional Review Board of the Sun Yat-sen Memorial Hospital affiliated to Sun Yat-sen University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The work described was original research that has not been published previously, and

not under consideration for publication elsewhere, in part or in whole. All authors believe that the manuscript represents valid work and have reviewed and approved the final version. Main document data and additional unpublished data from the study are available by sending Email to skendo@163.com with proper purposes.

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