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Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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1 **ABSTRACT**

2 **Objectives:** This study aimed to investigate the applicability of lipid accumulation

3 product (LAP) in the Southern Chinese population and compare the predictive effects

4 of LAP and other obesity indicators on hypertension risk. Moreover, this study

5 investigated the interactive effects of LAP and family history of hypertension.

6 **Methods:** A total of 2079 community-dwelling adults in Southern China were

7 enrolled in this cross-sectional study. The participants underwent the questionnaire

8 survey, anthropometric tests, and laboratory examinations. The multivariate logistic

9 regression model and receiver operating characteristic (ROC) curves were used to

10 assess the association between hypertension risk and obesity indexes, including LAP,

11 body mass index (BMI) and waist-hip ratio (WHR). The interaction effects were

12 evaluated by relative excess risk of interaction (RERI), attributable proportion due to

13 interaction (AP), and synergy index (SI).

14 **Results:** Higher LAP levels had relatively higher risk of hypertension (adjusted odds

15 ratio [OR] = 3.19 per SD increase; 95% confidence interval [CI] = 1.90–5.35; $P <$

16 0.001). LAP (area under curve [AUC] = 0.721; 95% CI: 0.680–0.761) was a better

17 indicator in indentifying hypertension risk than BMI (AUC = 0.698; 95% CI: 0.658–

18 0.737) and WHR (AUC = 0.684; 95% CI: 0.643–0.726) in females, but BMI

19 performed better in males. A significant interaction between LAP and family history

20 of hypertension was observed in males (RERI = 1.652, 95% CI: 0.267–3.037; AP =

21 0.516, 95% CI: 0.238–0.794; SI = 3.998, 95% CI: 0.897–17.820) but not in females.

22 **Conclusions:** LAP was significantly associated with the hypertension risk in the

23 Southern Chinese population, and LAP performed better on hypertension risk than did

24 BMI and WHR in the Southern China female population. The synergistic effect of

25 LAP and family history of hypertension was demonstrated in males, but further

26 studies are needed to investigate in females.

27 **Keywords: Hypertension, LAP, Family history, Interaction effect**

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1 **Strengths and limitations of this study**

2 To the best of our knowledge, our study is the first to examine the validity of LAP,

3 which was calculated using a modified formula, in the Southern China population. In

4 addition, this study has some limitations. First, because this is a cross-sectional study,

5 the results are not sufficient to indicate causality. Second, because of the small sample

6 size in this study, further studies with a larger sample size are needed to investigate

7 whether the modified LAP applies to all the residents dwelling in Southern China.

4

1 **INTRODUCTION**

2 Hypertension, a significant risk factor of cardiovascular disease,[1] is one of the most

3 prevalent public health problems in the world, and it is the leading contributor to the

4 global burden of disease and mortality. Nowadays, one-third of adults are suffering

5 from hypertension in China, and the number of adults with hypertension in the world

6 is being predicted to increase by about 60% to a total of 1.56 billion in 2025.[2, 3]

7 Accumulating evidence proves that obesity, especially visceral fat, and family

8 history of hypertension could significantly contribute to hypertension.[4-6] Numerous

9 studies have demonstrated that positive family history is an important risk factor for

10 hypertension.[6-9] When it comes to obesity, the indexes that are most frequently used to

11 assess obesity are body mass index (BMI), waist circumference (WC), and waist-hip

12 ratio (WHR); however, these traditional obesity indexes can merely reflect the

13 degrees of overweight and abdominal obesity but cannot distinguish between

14 subcutaneous fat and visceral fat.[10] Micromagnetic resonance imaging and

15 microcomputed tomography, the gold standard measurement methods of visceral fat,

16 are not only inconvenient but also expensive;[11] moreover, they are not suitable for

17 large-scale epidemiological investigations. Therefore, it is necessary for us to identify

18 a new obesity indicator that can distinguish visceral fat from subcutaneous fat

19 conveniently and economically.

20 Recently, increasing attention has been directed towards lipid accumulation product

21 (LAP). LAP, a new obesity index computed from WC and triglyceride (TG), has been

22 shown to be a useful indicator of visceral fat,[12] as demonstrated by Kahn in 2005[13].

23 Some studies suggest that LAP can also be used to identify metabolic syndromes,[14]

24 type 2 diabetes mellitus,[15] and stroke.[16]Additionally, several cross-sectional studies

25 conducted in Japan,[17] India,[14] and Brazil indicate that LAP is significantly associated

26 with cardiovascular disease and is a better indicator than BMI for identifying the

27 cardiovascular risk.[13, 18] A few national studies have investigated the association

28 between LAP and hypertension in China, and all of them were conducted in northern

29 China, including Bengbu,[19] Beijing,[20] and Inner Mongolia.[21] Owning to considerable

1 differences in climate, environment, and lifestyle between the south area and the north

2 area of China, the prevalence of hypertension and the levels of LAP should be

3 different. However, rare studies have compared LAP with other obesity indexes in the

4 Southern Chinese population. In addition, almost all studies about LAP used the

5 formula that was developed based on the third National Health and Nutrition

6 Examination Survey in the US. Therefore, it is reasonable to suggest that the

7 calculation formula of LAP needs to be modified in the Chinese population.

8 To the best of our knowledge, no studies have attempted to adjust the calculation

9 formula of LAP so that it can apply to the Southern Chinese population, and rare

10 studies have explored additive interactions between family history of hypertension

11 and LAP. Thus, the primary purpose of this study was to assess interactive effects

12 between adjusted LAP and family history of hypertension to predict the hypertension

13 risk in the Southern Chinese population.

METHODS

Study design and subjects

16 A cross-sectional survey based on community health was conducted in Southern

17 China. Recruiting the enrollors took place in March 2017. The study samples were

18 selected by a multistage and stratified random sampling method. A total of 3760

19 individuals were enrolled in this study; among them, 1681 participants who lacked

20 complete data on demographic characteristics, anthropometric tests, or laboratory

21 examinations were excluded. Finally, 2079 adults who had complete data were

22 included in the analysis.

Patient and public involvement

24 Patients or public were not involved in this study.

Ethics statement

26 This study was approved by the Ethics Committee of Guangzhou Medical University.

27 Written informed consent was obtained from each study participant before

28 investigation.

1 **General study questionnaire**

2 An interview-based survey was performed using a questionnaire by trained staff.

3 Socio-demographic data, family history of hypertension, cigarette smoking, and

4 alcohol drinking were investigated. Smokers were defined as the participants smoking

5 at least 1 cigarette/day for at least 6 months. Drinkers were defined as individuals

6 consuming at least 30 ml alcohol/week for 1 year or more. Physical activities were

7 divided into "seldom or never," "moderate," and "high." Participants with "seldom or

8 never" were defined as those who performed activity less than 2 times per week.

9 Participants with "moderate" were defined as those who exercised for more than 30

10 minutes each time, 3–5 times per week. Participants with "high" were defined as

11 those who exercised for more than 30 minutes each time, more than 6 times per week.

12 Marital status was classified as "currently not married" and "currently married";

13 "married" was regarded as "currently married," and "divorced/widowed/single" was

14 regarded as "currently not married." Educational level was categorized as "elementary

15 school or lower," "secondary school," and "senior high school or higher."

16 **Anthropometric tests and laboratory examinations**

17 The participants were required to take off their shoes and wear lightweight clothing

18 for weight and height measurements. WC was measured at the level of 1 cm above the

19 navel.[22] Automatic sphygmomanometer (OMRON, hem-7125) was used to measure

20 blood pressure (BP) of participants. BP measurement was conducted thrice in a quiet

21 environment, and the participants rested at least one minute between each time of

22 measurement. The mean of the three measurements was used in the analysis.

23 Prehypertension was defined as systolic blood pressure (SBP) of 120–139 mmHg

24 and/or diastolic blood pressure (DBP) of 80–89 mmHg, and hypertension was defined

25 as SBP of $\geq$ 140 mmHg, DBP of $\geq$ 90 mmHg, and/or a reported medical history of

26 anti-hypertensive medication.[22] The BMI was calculated as weight in kilograms

27 divided by the square of the height in meters. Overweight was defined as BMI of 24–

28 27.9 kg/m^2, and obesity was defined as BMI of $\geq$ 28 kg/m^2. The fasting blood samples

29 were collected from the participants in the morning after an overnight fast and were

1   used to assess fasting plasma glucose, total cholesterol, and TG levels.

2   According to Kahn's theory,[13] LAP is calculated as [WC (cm) - The minimum of

3   WC (male)] × [TG (mmol/L)] for males and [WC (cm) - The minimum of WC

4   (female)] × [TG (mmol/L)] for females, and the minimum waist size theoretically

5   contains only the abdomen, muscle, viscera, and vertebral bone.[13] Visceral fat can be

6   estimated by the difference between the WC and the minimum waist size. In the

7   present study, the WC of the studied population was skewed; therefore, the WC was

8   log-transformed. The minimum WC was estimated by the mean WC minus two

9   standard deviations after log-transformation in the local participants aged 18–24

10 years.[13, 20]

11 **Statistical analyses**

12 According to the hypertension status, the enrollees were divided into three groups

13 (normotension, prehypertension, and hypertension). The frequency (%) was used to

14 describe sex, marital status, education level, physical activity, BMI, smoker, and

15 drinker. Mean ± standard deviation (SDs) was used to describe the WHR, fasting

16 plasma glucose, total cholesterol, TG, SBP, DBP, and LAP. LAP was divided into

17 four groups by the quartiles, i.e., Q1, Q2, Q3, and Q4. The differences of quantitative

18 data across different hypertension statuses were analyzed by the Kruskal-Wallis H test

19 because the data had skewed distribution. Categorical variables were analyzed by the

20 Chi-squared test. The multivariate logistic regression model was used to analyze the

21 relationship between LAP and risk factors of hypertension and prehypertension. The

22 receiver operating characteristics (ROC) curves were applied to identify the superior

23 obesity index and the best cut-off value of LAP to predict the hypertension risk.

24 Moreover, the interaction effects between LAP and family history of hypertension

25 were assessed by some relevant indicators, including the relative excess risk of

26 interaction (RERI = OR_{11} - OR_{10} - OR_{01} + 1), the attributable proportion due to

27 interaction (AP = [OR_{11} - OR_{10} - OR_{01} + 1]/OR_{11}), and the synergy index (SI = [OR_{11} -

28 1]/[OR_{01} - 1] + [OR_{10} - 1]). If the interaction effect was not observed, the confidence

29 interval of RERI and AP contained 0 and the confidence interval of S included 1.[23]

1   The above indicators were calculated using an Excel table designed by Andersson et

2   al..[23] All reported *P*-values were two-tailed, and a *P*-value of < 0.05 was considered

3   significant. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc.,

4   Chicago, IL, USA).

5   **RESULTS**

6   **LAP**

7   According to Kahn's theory,[13] LAP was calculated as (WC - 60.6) × (TG [mmol/L])

8   in males and (WC - 54.1) × (TG [mmol/L]) in females based on the actual data

9   obtained from the Southern Chinese population (Table 1).[20]

Basic characteristics of the study participants

11   A total of 2079 adults with an average age of 41.06 years were enrolled in the present

12   study, including 1002 males (48.29%) and 1077 females (51.80%). The overall

13   prevalence rates of normotension, prehypertension, and hypertension were 40.02%,

14   37.95%, and 22.03%, respectively. Male participants had a high prevalence of

15   prehypertension and hypertension than female participants ($P < 0.001$). Statistically

16   significant differences in age ($P < 0.001$), marital status ($P < 0.001$), education level

17   ($P < 0.001$), smoker ($P < 0.001$), drinker ($P < 0.001$), and family history of

18   hypertension ($P = 0.005$) were observed between normotension, prehypertension, and

19   hypertension groups. However, no significant differences were observed in physical

20   activity ($P = 0.611$) among the three groups. Anthropometric measurements found

21   significant differences in BMI ($P < 0.001$), WHR ($P < 0.001$), LAP ($P < 0.001$),

22   fasting plasma glucose ($P < 0.001$), total cholesterol ($P < 0.001$), SBP ($P < 0.001$),

23   and DBP ($P < 0.001$) between the groups (Table 2).

LAP and the risk factors of hypertension

25   In order to investigate the relationship between LAP and blood pressure, LAP was

26   divided into four groups by quartile (Table 3). A significant association was observed

27   between LAP and blood pressure. SBP ($P < 0.001$) and DBP ($P < 0.001$) were

28   relatively elevated in participants with higher LAP levels.

1 Multinomial logistic regression analysis was conducted to evaluate the association

2 between LAP quartiles and hypertension status (Table 4). Participants with the fourth

3 quartile of LAP were more likely to develop prehypertension (crude OR = 6.23, 95%

4 CI: 4.54–8.54) and hypertension (crude OR = 21.22, 95% CI: 14.02–32.09) than those

5 with the first quartile. Moreover, after adjusting for age, sex, marital status,

6 educational level, physical activity, smoker, drinker, BMI, and WHR, the risks of

7 prehypertension (adjusted OR: 2.34, 95% CI: 1.58–3.48) and hypertension (adjusted

8 OR: 3.52; 95% CI: 2.11–5.88) significantly increased in participants with the fourth

9 quartile compared with those with the first quartile. After controlling for age, sex,

10 marital status, educational level, physical activity, smoker, drinker, BMI, WHR,

11 fasting plasma glucose, and family history of hypertension, increased risks of

12 prehypertension (adjusted OR: 2.25, 95% CI: 1.51–3.35) and hypertension (adjusted

13 OR: 3.19, 95%CI: 1.90–5.35) were observed in participants with the fourth LAP

14 quartile compared with those with the first one.

15 The results of ROC curves analysis in males and females are shown in Figs. 1 and 2

16 and Table. 5. LAP (AUC = 0.721; 95% CI: 0.680–0.761) was a better indicator to

17 discriminate between different types of hypertension than BMI (AUC = 0.698; 95%

18 CI: 0.658–0.737) or WHR (AUC = 0.684; 95% CI: 0.643–0.726) in females;

19 however, BMI (AUC = 0.707, 95% CI: 0.672–0.742) performed better than WHR

20 (AUC = 0.688; 95% CI: 0.650–0.725) and LAP (AUC = 0.677; 95% CI: 0.640–0.713)

21 in males. The best cut-off values to predict hypertension were 63.892 in males and

22 30.860 in females.

Interaction effects between LAP and family history of hypertension

23

24 The interaction effects between LAP and family history of hypertension are presented

25 in Table 6. Significant interaction effects between LAP and family history of

26 hypertension were observed in males. The results of RERI (1.652; 95% CI: 0.267–

27 3.037) and AP (0.516; 95% CI: 0.238–0.794) indicated a significant interaction effect

28 of family history of hypertension and LAP on hypertension, but the result of SI

29 (3.998; 95% CI: 0.897–17.820) did not.

1   However, no significant interaction effects were found between LAP and family

2 history of hypertension in females, as indicated by all the three indicators. RERI was

3 - 0.673 (95% CI: -2.566–1.220); AP was -0.328 (95% CI: -1.451–0.795); and SI was

4 0.610 (95% CI: 0.125–2.979).

5 **Discussion**

6 With the rapid development of the economy, elevated blood pressure has become a

7 common and serious public health issue.[24] The prevalence of prehypertension and

8 hypertension has significantly increased.[25] Elevated blood pressure is caused by

9 diverse factors, among which obesity is closely related to hypertension.[26] Nowadays,

10 the prevalence of obesity has increased by 13% in urban areas and by 85% in rural

11 areas in China,[16] and more attention should thus be paid to this issue. An increase in

12 body weight is typically followed by enhanced blood pressure.[12] Extensive studies

13 have found that obesity, especially visceral adipose tissue, could strongly increase the

14 blood pressure.[26]

15   The mechanisms underlying the interaction between obesity and hypertension are

16 complicated. The mechanisms of obesity-induced hypertension include sodium

17 retention, insulin resistance, activation of renin-angiotensin-aldosterone, altered

18 vascular function, and secretion of relevant adipokines.[27] In addition, the mechanisms

19 of blood pressure increase can be activated by visceral fat.[28]

20   Substantial evidences proved that the harm of the fat accumulation was greater than

21 the total amount of fat.[29, 30]However, traditional obesity indexes, such as BMI, WC,

22 and WHR, have some limitations when distinguishing between subcutaneous fat and

23 visceral fat. Therefore, a new obesity index that can distinguish visceral fat easily and

24 effectively is urgently needed. After Kahn first demonstrated that LAP performs

25 better than BMI for recognizing the cardiovascular risk, domestic and foreign scholars

26 have paid increasing attention to LAP. LAP, a combination of WC and TG, is an

27 accessible and inexpensive way to assess visceral fat.[13] It is a well-known fact that TG

28 can reflect the degree of visceral fat accumulation and WC is strongly associated with

1 hypertension.[12] Notably, hypertriglyceridemic waist (HTGW) is also calculated based

2 on the combination of TG and WC. However, LAP, a continuous indicator, is superior

3 to reflect visceral fat than HTGW,[31] a dichotomous indicator.[19] Therefore, LAP was

4 used as a visceral obesity indicator in this study.

5 LAP based on hypothesis of minimum waist circumference includes the rachis,

6 abdominal viscera and muscle.[13] Therefore, the differences between the actual WC

7 and the minimum WC can represent abdominal adipose tissue.[13] Notably, LAP in

8 almost all studies is calculated by data obtained based on the third National Health

9 and Nutrition Examination Survey in the United States.[13] Because of differences in

10 race, dietary habits, or lifestyle, individuals from different countries should have

11 different visceral adipose tissues. It has been demonstrated that there are considerable

12 differences in visceral adipose tissues between Chinese individuals and Europeans or

13 Americans.[32] Therefore, LAP was calculated in our study using a modified formula so

14 that it could apply to the individuals dwelling in Southern China.

15 As expected, a significant association was found between LAP and hypertension in

16 this present study. Our findings are consistent with those in studies by Zhong et al,[16]

17 Song et al,[30] and Shen et al,[20] all of which have demonstrated that LAP is an effective

18 and reliable diagnostic indicator of hypertension. Participants with significantly

19 higher LAP had higher risks of prehypertension and hypertension than those with

20 lower LAP. Multinomial logistic regression analysis revealed that after adjusting for

21 other factors, the risks of prehypertension and hypertension in the group with the

22 highest LAP level were 2.25 and 3.19 times higher, respectively, than those in the

23 group with the lowest LAP.

24 In the present study, we also found that LAP was a better indicator than BMI and

25 WHR for identifying the risk of hypertension in females, but BMI was slightly

26 superior to LAP in males. Because women are more likely to accumulate adipose

27 tissue around the hips and thighs, we can easily understand why LAP is superior to

28 BMI in identifying the risk of hypertension in females.[33] Similar results have been

29 obtained in the study by Wang et al..[34] However, Gao et alfound that the performance

1   of LAP was superior to that of BMI in male Mongolians;[21] the findings may be due to

2   the apparently lower prevalence of high TG in female Mongolians than in male

3   Mongolians ($P < 0.05$), and the facts might disturb the association between LAP and

4   hypertension in female Mongolians.

5   In general, LAP, which applied to the Southern Chinese population, was a better

6   indicator for predicting the hypertension risk in this study. In addition, large studies

7   have demonstrated that family history of hypertension is a critical risk factor for

8   hypertension, and individuals with family history of hypertension are 2–4 times more

9   likely to develop hypertension than those without the family history of hypertension.[35]

10   The interaction analysis in this study indicates the synergistic effect of LAP and

11   family history on the hypertension risk in males, but not in females. In fact,

12   cardiovascular events occur at a lower rate in females than in males.[36] In our study,

13   the feminine participants who suffered both LAP and family history of hypertension

14   were rarely observed and the prevalence rates of hypertension at a lower rate in

15   females than in males.[36] Fewer positive observers in female might be due to sampling

16   error, but might disturb the interaction effect between LAP and family history of

17   hypertension on the hypertension risk in females. Visceral obesity and family history

18   of hypertension may result in increased blood pressure through some unknown

19   mechanisms. The synergistic effect between family history of hypertension and LAP

20   on the hypertension risk was demonstrated in our study as well as in other studies.[19, 34]

21   However, further studies are needed to investigate the interaction effect between LAP

22   and family history of hypertension on the hypertension risk.

23   To date, LAP is an inexpensive screening tool to identify visceral adipose tissue,

24   and the method has high reproducibility. LAP, which was proposed by Kahn, was

25   developed for the Western population.Thus this study explored the validity of LAP,

26   which was calculated based on the Southern China population. The findings suggest

27   LAP might perform better in predicting the hypertension risk than BMI and WHR in

28   Southern Chinese females.

29   This study has some limitations. First, because this is a cross-sectional study, the

present results are not sufficient to indicate causality. Second, because of the small sample size in this study, further studies with a larger sample size are needed to investigate whether the modified LAP applies to all the residents dwelling in Southern China.

CONCLUSION

In conclusion, LAP can be used to distinguish visceral fat from subcutaneous fat in the Southern Chinese population. LAP was significantly associated with the hypertension risk, and higher LAP levels had relatively higher blood pressure. LAP performed better in predicting hypertension than did BMI and WHR in the Southern China female population. The synergistic effect of LAP and family history of hypertension was demonstrated in males, and further studies are needed to investigate the interactive effects between LAP and family history of hypertension in females.

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Contributors

Jun-Xuan Huang, Pei-Xi Wang and Jin-Xiang Ma conceived and designed the study. Jun-Xuan Huang, Xin-Yu Bao, Yi-Xian Xie, Xiao-Xia Zhang, Xin Peng, Yan Liu and Meng-Jiao Cheng contributed to collection of the data, analyzed the data and interpretation of the results. Jun-Xuan Huang wrote the draft manuscript. Jin-Xiang Ma, Pei-Xi Wang and Jun-Xuan Huang finalized the manuscript. All of the authors approved the final version submitted for publication.

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1 **Competing interests**

2 The authors declared that they had no conflict of interest.

3 **Ethics statement**

4 This study was approved by the Ethics Committee of Guangzhou Medical University.

5 Written informed consent was obtained from each study participant before

6 investigation.

7 **Data sharing statement**

8 Our data might not be shared directly, because data belongs to all the team members

9 and informed consent should be attained from team members.

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The titles and legends of figure

Title

Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio.

Title

Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio.

20

1   **Table 1** The theoretically minimum waist size in the Southern Chinese population

Sex	Log-transformed waist (cm)	Theoretically minimum waist (cm)
Male	4.328 ± 0.112	60.6
Female	4.255 ± 0.134	54.1

2

3   **Table 2** Basic characteristics of the participants

Variables	Normotension (N = 832)	Prehypertension (N = 789)	Hypertension (N = 458)	χ^2 / Z	*P*-value
Sex (%)				135.625	< 0.001
Male	32.57	58.68	58.52		
Female	67.43	41.32	41.48		
Age (years)	36.42 ± 10.59	41.38 ± 12.71	48.93 ± 12.75	267.206	< 0.001
Marital status (%)				21.287	< 0.001
Currently not married	23.20	18.76	12.66		
Currently married	76.80	81.24	87.34		
Education level (%)				101.355	< 0.001
Elementary school and lower	15.87	21.55	36.46		
Secondary school	36.30	38.53	39.96		
Senior high school and higher	47.83	39.92	23.58		
Physical activity (%)				2.688	0.611
Seldom or never	35.70	34.22	31.22		
Moderate	17.43	18.25	18.78		
High	46.87	47.53	50.00		

Smoker (%)				50.346	< 0.001
Non-smoker	82.25	71.61	67.90		
Smoker	16.18	26.87	28.61		
Former smoker	0.97	1.52	3.49		
Drinker (%)				30.865	< 0.001
Non-drinker	84.11	76.34	72.53		
Drinker	14.91	22.39	24.62		
Former drinker	0.98	1.27	2.85		
BMI				255.012	< 0.001
< 18.5	13.70	5.20	2.18		
18.5–23.9	68.51	54.88	41.70		
24–27.9	14.30	31.69	37.55		
≥ 28	3.49	8.24	18.56		
WHR				248.475	< 0.001
Fasting plasma glucose (mmol/L)	4.69 ± 0.82	4.98 ± 1.33	5.31 ± 1.86	90.399	< 0.001
Total cholesterol (mmol/L)	4.70 ± 0.96	4.98 ± 1.07	5.26 ± 1.15	88.325	< 0.001
Triglyceride (mmol/L)	1.26 ± 0.83	1.77 ± 1.77	2.15 ± 2.25	178.995	< 0.001
Systolic blood pressure (mmHg)	107.97 ± 7.80	125.45 ± 6.65	144.78 ± 18.55	1533.137	< 0.001
Diastolic blood pressure (mmHg)	69.49 ± 6.40	79.59 ± 5.99	91.49 ± 11.33	1206.505	< 0.001
Family history of hypertension (%)				18.391	0.005
Only father	11.42	11.03	11.14		
Only mother	12.02	15.08	17.25		
Both parents	5.41	4.82	8.95		

Neither	71.15	69.07	62.66		
LAP	29.14 ± 27.00	52.15 ± 63.50	75.87 ± 99.81	355.133	< 0.001

1   BMI: body mass index; WHR: waist-hip rate; LAP: lipid accumulation product.

2

3   **Table 3** Comparison of blood pressure among four quartiles of LAP

	LAP				Z	*P*-value
Variables	**Q1**	**Q2**	**Q3**	**Q4**		
	(< 17.36)	**(17.36–31.31)**	**(31.31–57.46)**	**(> 57.46)**		
Systolic blood pressure (mmHg)	112.47 ± 13.63	119.74 ± 15.12	125.85 ± 15.96	132.71 ± 19.09	405.625	< 0.001
Diastolic blood pressure (mmHg)	71.93 ± 9.31	76.66 ± 10.50	79.68 ± 10.04	84.37 ± 11.59	354.672	< 0.001

4

5   **Table 4** Multinomial logistic regression analysis of LAP associated with hypertension status

	OR[a](95% CI)		OR[b](95% CI)		OR[c](95% CI)	
Quartiles of LAP	**prehypertension**	**hypertension**	**prehypertension**	**hypertension**	**prehypertension**	**hypertension**
Q1 (< 17.36)	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2 (17.36–31.31)	2.83*** (1.73, 3.01)	3.10*** (2.04, 4.72)	1.64** (1.19, 2.17)	1.51 (0.95, 2.40)	1.61** (1.19, 2.18)	1.53 (0.96, 2.43)
Q3 (31.31–57.46)	4.41*** (3.32, 5.87)	7.85*** (5.22, 11.82)	2.20*** (1.67, 3.08)	2.00** (1.23, 3.23)	2.18*** (1.56, 3.07)	1.89** (1.16, 3.07)
Q4 (> 57.46)	6.23*** (4.54, 8.54)	21.22*** (14.02, 32.09)	2.34*** (1.58, 3.48)	3.52*** (2.11, 5.88)	2.25*** (1.51, 3.35)	3.19*** (1.90, 5.35)

1   OR=Odds ratio; CI=confidence interval; [***], $P < 0.001$; [**], $P < 0.01$; [*], $P < 0.05$.

2   [a], unadjusted.

3   [b], adjusted for age, sex, marital status, educational level, physical activity, smoker, drinker, BMI,

4   and WHR.

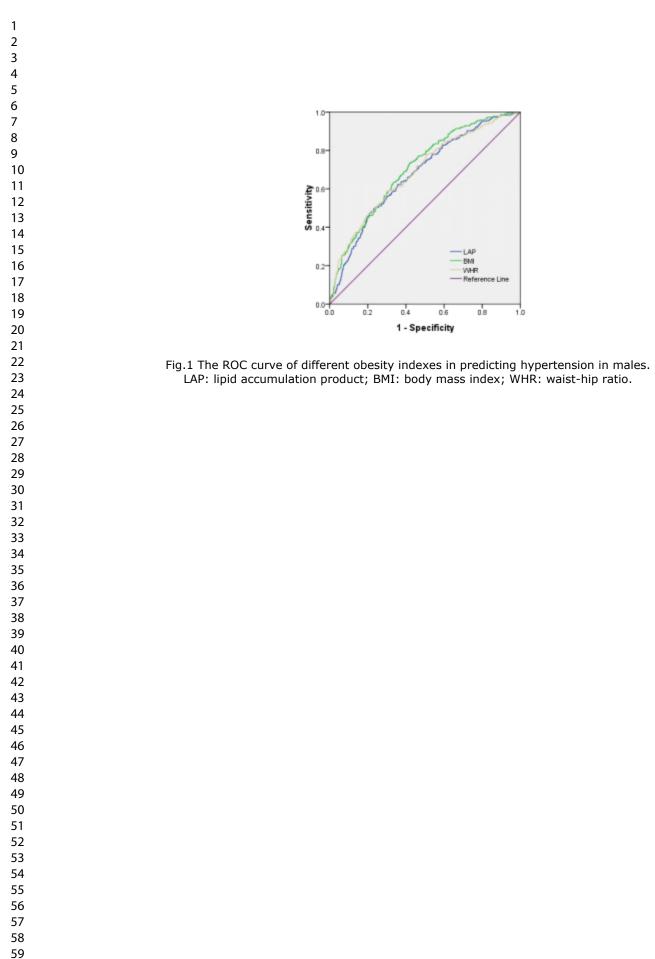5   [c], adjusted for fasting plasma glucose, family history of hypertension, and all the factors in b.

6

7   **Table 5** Predicting hypertension by different obesity indexes

Variables	Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index	AUC(95% CI)	*P*-value
Male						
BMI	23.004	0.735	0.581	0.316	0.707 (0.672, 0.742)	< 0.001
WHR	0.906	0.586	0.703	0.289	0.688 (0.650, 0.725)	< 0.001
LAP	63.892	0.496	0.770	0.266	0.677 (0.640, 0.713)	< 0.001
Female						
BMI	21.767	0.816	0.507	0.323	0.698 (0.658, 0.737)	< 0.001
WHR	0.860	0.742	0.552	0.294	0.684 (0.643, 0.726)	< 0.001
LAP	30.860	0.689	0.674	0.363	0.721 (0.680, 0.761)	< 0.001

8   BMI: body mass index; WHR: waist-hip rate; LAP: lipid accumulation product; AUC: area under

9   curve; OR=Odds ratio; CI=confidence interval.

10

11   **Table 6** Interaction effects between LAP and family history of hypertension

Variables	Variables	N	OR[c] (95% CI)	Interaction indexes (95% CI)
Male				
LAP[a]	Family history[b]			
-	-	486	1 (reference)	RERI = 1.652 (0.267, 3.037)[*]

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-	+	215	1.189 (0.772, 1.832)	AP = 0.516 (0.238, 0.794)[*]
+	-	173	1.362 (0.875, 2.121)	SI = 3.998 (0.897, 17.820)
+	+	128	3.203[***] (2.002, 5.124)	

Female

LAP[a]	Family history[b]			
-	-	657	1 (reference)	RERI = -0.673 (-2.566, 1.220)
-	+	276	1.995[**] (1.284, 3.099)	AP = -0.328 (-1.451, 0.795)
+	-	108	1.729[*](1.023, 2.922)	SI = 0.610 (0.125, 2.979)
+	+	36	2.051 (0.919, 4.589)	

1   LAP: lipid accumulation production; RERI: relative excess risk of interaction ; AP:

2   attributable proportion due to interaction; SI: synergy index; OR=Odds ratio;

3   CI=confidence interval; [***], $P < 0.001$; [**], $P < 0.01$; [*], $P < 0.05$.

4   [a], grouped by the cut-off values in Table 5.

5   [b], family history of hypertension was defined as one parent or both parents having hypertension.

6   [c], adjusted for age, marital status, educational level, physical activity, smoker, drinker, BMI,

7   and WHR.

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Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.
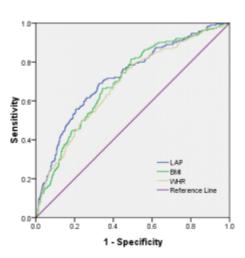LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio.

Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 6

Study size	10	Explain how the study size was arrived at	Page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7-8
		(*c*) Explain how missing data were addressed	Page 5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8; Table 2
		(b) Give reasons for non-participation at each stage	Not application
		(c) Consider use of a flow diagram	Not application
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8; Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Not application
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8; Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-10; Table 4; Table 6
		(*b*) Report category boundaries when continuous variables were categorized	Page 6-8; Table 2;

			Table 3 ; Table 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not application
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 9-10; Table 6
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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1

Interaction of lipid accumulation product and family history of hypertension on

hypertension risk: A cross-sectional study in the Southern Chinese population

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1   **ABSTRACT**

2   **Objectives:** This study aimed to investigate the applicability of a novel index based

3   on WC and TG, named lipid accumulation product (LAP) in the Southern Chinese

4   population, and compare the predictive effects of LAP and other obesity indicators on

5   hypertension risk. Moreover, this study investigated the interactive effects of LAP and

6   family history of hypertension.

7   **Methods:** A total of 2079 community-dwelling adults in Southern China were

8   enrolled in this cross-sectional study. The participants underwent the questionnaire

9   survey, anthropometric tests, and laboratory examinations. The multivariate logistic

10 regression model and receiver operating characteristic (ROC) curves were used to

11 assess the association between hypertension risk and obesity indexes, including LAP,

12 body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC),

13 Triglyceride (TG). The interaction effects were evaluated by relative excess risk of

14 interaction (RERI), attributable proportion due to interaction (AP), and synergy index

15 (SI).

16 **Results:** Higher LAP levels had relatively higher risk of hypertension in both sex

17 (males: adjusted odds ratio [OR] = 2.79 per SD increase, 95% confidence interval [CI]

18 = 1.43-5.44, $P < 0.001$; females: adjusted OR:3.15,95%CI=1.56-6.39, $P < 0.001$).

19 LAP (area under curve [AUC] = 0.721; 95% CI: 0.680–0.761) was a better indicator

20 in identifying hypertension risk than BMI, WHR and TG in females, but WC

21 performed better in males. A significant interaction between LAP and family history

22 of hypertension was observed in males (RERI = 1.652, 95% CI: 0.267–3.037; AP =

23 0.516, 95% CI: 0.238–0.794; SI = 3.998, 95% CI: 0.897–17.820), but no statisitically

24 significant differences in females.

25 **Conclusions:** LAP was significantly associated with the hypertension risk in the

26 Southern Chinese population, and LAP performed better on hypertension risk than did

27 BMI, WHR and TG in the Southern China females population. The synergistic effect

28 of LAP and family history of hypertension was demonstrated.

1   **Keywords: Hypertension, LAP, Family history, Interaction effect**

2   **Strengths and limitations of this study**

3   **Strengths**:

4   1. Our study is the first to examine the validity of LAP, which was calculated using a

5   modified formula, in the Southern China population.

6   **Limitations:**

7   1. This is a cross-sectional study, the results are not sufficient to indicate causality.

8   2. The population of our study can partially represent the general population in the

9   Southern China, but cannot fully represent this region.

10   3. Lack of the adjustment for renal function, and other risk factors for hypertension

11   (such as serum uric acid) in our study.

12   4. This study has small sample size, so further studies with a larger sample size are

13   needed to investigate whether the modified LAP applies to all the residents dwelling

14   in Southern China.

4

1 **INTRODUCTION**

2 Hypertension, a significant risk factor of cardiovascular disease,[1] is one of the most

3 prevalent public health problems in the world, and it is the leading contributor to the

4 global burden of disease and mortality. Nowadays, the number of adults with

5 hypertension in the world is being predicted to increase by about 60% to a total of

6 1.56 billion in 2025, and one-third of adults are suffering from hypertension in

7 China.[2, 3]

8 Accumulating evidence proves that obesity, especially visceral fat, and family

9 history of hypertension could significantly contribute to hypertension.[4-6] Numerous

10 studies have demonstrated that positive family history is an important risk factor for

11 hypertension.[6-9] When it comes to obesity, the indexes that are most frequently used to

12 assess obesity are body mass index (BMI), waist circumference (WC), and waist-hip

13 ratio (WHR); however, these traditional obesity indexes can merely reflect the

14 degrees of overweight and abdominal obesity but cannot distinguish between

15 subcutaneous fat and visceral fat.[10] Micromagnetic resonance imaging and

16 microcomputed tomography, the gold standard measurement methods of visceral fat,

17 are not only inconvenient but also expensive;[11] moreover, they are not suitable for

18 large-scale epidemiological investigations. Therefore, it is necessary for us to identify

19 a new obesity indicator that can predict visceral fat from subcutaneous fat

20 conveniently and economically.

21 Recently, increasing attention has been directed towards lipid accumulation product

22 (LAP). LAP, a new obesity index computed from WC and triglyceride (TG), has been

23 shown to be a useful indicator of visceral fat,[12] as demonstrated by Kahn in 2005[13].

24 Some studies suggest that LAP can also be used to identify metabolic syndromes,[14,15]

25 type 2 diabetes mellitus,[16] stroke[17] and arterial stiffness.[18] Additionally, several

26 cross-sectional studies conducted in Japan,[19] India,[14] and Brazil indicate that LAP is

27 significantly associated with cardiovascular disease and is a better indicator than BMI

28 for identifying the cardiovascular risk.[13, 20] A few national studies have investigated

29 the association between LAP and hypertension in China, and all of them were

1   conducted in northern China, including Bengbu,[21] Beijing,[22] and Inner Mongolia.[23]

2   With a vast territory, China has tremendous difference between South and North. Due

3   to the geographical environment and dietary habits that have formed throughout its

4   long history, there are some dietary and cultural differences between Northern and

5   Southern China.[24] The Northern region shows a high intake of wheat, tubers and

6   liquor,etc. While southerner has a high intake of rice, vegetables, meat, poultry, fish

7   etc.[24] The Carbohydrate-rich pattern of the northern region is associated with a high

8   risk of hypertriglyceridemia and higher BMI. Meanwile, significant differences are

9   found in SBP/DBP between southern Chinese and northern Chinese owing to

10   different climate and dietary habit between southern and northern.[25] Studies have

11   found that the northerners were heavier and had higher triglycerides level than

12   southerners.[26,27] Differences in dietary habits, or lifestyle, individuals from different

13   regions should lead to different LAP. LAP has a different situation in the north and

14   south. Thus, the applicability of LAP in predicting hypertension in Southern China is

15   worth studying. However, rare studies have compared LAP with other obesity indexes

16   in the Southern Chinese population. In addition, almost all studies about LAP used the

17   formula that was developed based on the third National Health and Nutrition

18   Examination Survey in the US. Therefore, it is reasonable to suggest that the

19   calculation formula of LAP needs to be modified in the Chinese population.

20   To the best of our knowledge, no studies have attempted to adjust the calculation

21   formula of LAP so that it can apply to the Southern Chinese population, and rare

22   studies have explored additive interactions between family history of hypertension

23   and LAP. Thus, the primary purpose of this study was to investigate the applicability

24   of LAP in the Southern Chinese population and compare the predictive effects of LAP

25   and other obesity indicators on hypertension risk. And the secondary purpose of the

26   study was to assess interactive effects between LAP and family history of

27   hypertension to predict the hypertension risk in the Southern Chinese population.

28   **METHODS**

29   **Study design and subjects**

6

1   A cross-sectional survey based on community health was conducted in the FoShan

2   city of Guangdong province in the Southern China. Recruiting the enrollors took

3   place in March 2017. The study samples were selected by a multistage and stratified

4   random sampling method. The stratification according to the economic level and

5   randomly selected street communities at economic levels, then randomly selected

6   communities in street communities according to proportion. Communities residents

7   were then randomly selected from the household lists. A total of 3760 individuals

8   were enrolled in this study; among them, 1681 participants who lacked complete data

9   on demographic characteristics, anthropometric tests, or laboratory examinations were

10   excluded. Finally, 2079 adults who had complete data were included in the analysis.

11   **Patient and public involvement**

12   Patients or public were not involved in this study.

13   **Ethics statement**

14   This study was approved by the Ethics Committee of Guangzhou Medical University.

15   Written informed consent was obtained from each study participant before

16   investigation.

17   **General study questionnaire**

18   An interview-based survey was performed using a questionnaire by trained staff.

19   Socio-demographic data, family history of hypertension, cigarette smoking, and

20   alcohol drinking were investigated. Smokers were defined as the participants smoking

21   at least 1 cigarette/day for at least 6 months. Drinkers were defined as individuals

22   consuming at least 30 ml alcohol/week for 1 year or more. Physical activities were

23   divided into "insufficiently active" and "sufficiently active." Participants with

24   "insufficiently active" were defined as those who performed activity less than

25   150min/week. Participants with "sufficiently active" were defined as those who

26   exercised more than 150min/week.[28] Marital status was classified as "currently not

27   married" and "currently married"; "married" was regarded as "currently married," and

28   "divorced/widowed/single" was regarded as "currently not married." Educational

1 level was categorized as "elementary school or lower," "secondary school," and

2 "senior high school or higher."

Anthropometric tests and laboratory examinations

4 The participants were required to take off their shoes and wear lightweight clothing

5 for weight and height measurements. WC was measured at the level of 1 cm above the

6 navel.[29] Automatic sphygmomanometer (OMRON, hem-7125) was used to measure

7 blood pressure (BP) of participants. BP measurement was conducted thrice in a quiet

8 environment, and the participants rested at least one minute between each time of

9 measurement. The mean of the three measurements was used in the analysis.

10 Prehypertension was defined as systolic blood pressure (SBP) of 120–139 mmHg

11 and/or diastolic blood pressure (DBP) of 80–89 mmHg, and hypertension was defined

12 as SBP of $\geq$ 140 mmHg, DBP of $\geq$ 90 mmHg, and/or a reported medical history of

13 anti-hypertensive medication.[29] The BMI was calculated as weight in kilograms

14 divided by the square of the height in meters. Overweight was defined as BMI of

15 24–27.9 kg/m^2, and obesity was defined as BMI of $\geq$ 28 kg/m^2. The fasting blood

16 samples were collected from the participants in the morning after an overnight fast

17 and were used to assess fasting plasma glucose, total cholesterol, and TG levels.

18 According to Kahn's theory,[13] LAP is calculated as [WC (cm) - The minimum of

19 WC (male)] $\times$ [TG (mmol/L)] for males and [WC (cm) - The minimum of WC

20 (female)] $\times$ [TG (mmol/L)] for females, and the minimum waist size theoretically

21 contains only the abdomen, muscle, viscera, and vertebral bone.[13] Visceral fat can be

22 estimated by the difference between the WC and the minimum waist size. In the

23 present study, the WC of the studied population was skewed; therefore, the WC was

24 log-transformed. The minimum WC was estimated by the mean WC minus two

25 standard deviations after log-transformation in the local participants aged 18–24

26 years.[13, 22]

Statistical analyses

28 According to the hypertension status, the enrollees were divided into three groups

1 (normotension, prehypertension, and hypertension). The frequency (%) was used to

2 describe sex, marital status, education level, physical activity, BMI, smoker, and

3 drinker. Mean ± standard deviation (SDs) was used to describe the WC, WHR, fasting

4 plasma glucose, total cholesterol, TG, SBP, DBP, and LAP. LAP was divided into

5 four groups by the quartiles, i.e., Q1, Q2, Q3, and Q4. The differences of quantitative

6 data across different hypertension statuses were analyzed by the Kruskal-Wallis H test

7 because the data had skewed distribution. Categorical variables were analyzed by the

8 Chi-squared test. The multivariate logistic regression model was used to analyze the

9 relationship between LAP and risk factors of hypertension and prehypertension. The

10 receiver operating characteristics (ROC) curves were applied to identify the superior

11 obesity index and the best cut-off value of LAP to predict the hypertension risk.

12 Moreover, the interaction effects between LAP and family history of hypertension

13 were assessed by some relevant indicators, including the relative excess risk of

14 interaction ($RERI = OR_{11} - OR_{10} - OR_{01} + 1$), the attributable proportion due to

15 interaction ($AP = [OR_{11} - OR_{10} - OR_{01} + 1]/OR_{11}$), and the synergy index ($SI = [OR_{11} -$

16 $1]/[OR_{01} - 1] + [OR_{10} - 1]$). If the interaction effect was not observed, the confidence

17 interval of RERI and AP contained 0 and the confidence interval of S included 1.[30]

18 The above indicators were calculated using an Excel table designed by Andersson et

19 al..[30] All reported *P*-values were two-tailed, and a *P*-value of < 0.05 was considered

20 significant. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc.,

21 Chicago, IL, USA).

22 **RESULTS**

23 **LAP**

24 According to Kahn's theory,[13] LAP was calculated as (WC - 60.6) × (TG [mmol/L])

25 in males and (WC - 54.1) × (TG [mmol/L]) in females based on the actual data

26 obtained from the Southern Chinese population .[22]

27 **Basic characteristics of the study participants**

28 A total of 2079 adults with an average age of 41.06 years were enrolled in the present

1 study, including 1002 males (48.29%) and 1077 females (51.80%). The overall

2 prevalence rates of normotension, prehypertension, and hypertension were 40.02%,

3 37.95%, and 22.03%, respectively. Male participants had a high prevalence of

4 prehypertension and hypertension than female participants ($P < 0.001$). Statistically

5 significant differences in age ($P < 0.001$), marital status ($P < 0.001$), education level

6 ($P < 0.001$), smoker ($P < 0.001$), drinker ($P < 0.001$), and family history of

7 hypertension ($P = 0.005$) were observed between normotension, prehypertension, and

8 hypertension groups. However, no significant differences were observed in physical

9 activity ($P = 0.550$) among the three groups. Anthropometric measurements found

10 significant differences in BMI ($P < 0.001$), WC ($P < 0.001$), WHR ($P < 0.001$), LAP

11 ($P < 0.001$) between the groups. And significant differences found in laboratory

12 examinations including fasting plasma glucose ($P < 0.001$), total cholesterol ($P <$

13 0.001), SBP ($P < 0.001$), and DBP ($P < 0.001$) between the groups (Table 1).

14 **LAP and the risk factors of hypertension**

15 In order to investigate the relationship between LAP and blood pressure, LAP was

16 divided into four groups by quartile in different sex (Table 2). A significant

17 association was observed between LAP and blood pressure in both male and female.

18 The results in male and female were shown that SBP ($P < 0.001$) and DBP ($P < 0.001$)

19 were relatively elevated in participants with higher LAP levels.

20 Multinomial logistic regression analysis was conducted to evaluate the association

21 between LAP quartiles and hypertension status (Table 3). Participants with the third

22 and the fourth quartile of LAP were more likely to develop prehypertension and

23 hypertension than those with the first quartile in both male and female.

24 After adjusting for age, marital status and educational level, the risks of

25 prehypertension (adjusted OR: 3.14, 95% CI: 1.95–5.07) and hypertension (adjusted

26 OR: 9.02; 95% CI: 5.11–15.93) significantly increased in male participants with the

27 fourth quartile compared with those with the first quartile. For the female, increased

28 risks of prehypertension (adjusted OR: 3.26, 95% CI: 2.09–5.10) and hypertension

29 (adjusted OR: 6.32; 95% CI: 3.42–11.65) were observed in participants with the

1   fourth LAP quartile compared with those with the first one.

2   After controlling for age, marital status, educational level, physical activity, smoker,

3   drinker, BMI, WHR, fasting plasma glucose and family history of hypertension, the

4   risks of prehypertension (adjusted OR: 1.67, 95% CI: 0.96–2.92) and hypertension

5   (adjusted OR: 2.79, 95%CI: 1.43–5.44) significantly increased in male participants

6   with the fourth quartile compared with those with the first quartile. Meanwhile,

7   increased risks of prehypertension (adjusted OR: 2.10, 95% CI: 1.26–3.51) and

8   hypertension (adjusted OR: 3.15, 95%CI: 1.56–6.39) were observed in female

9   participants with the fourth LAP quartile compared with those with the first one.

10   The results of ROC curves analysis in males and females were shown in Figs. 1 and

11   2 and Table 4. LAP (AUC = 0.721; 95% CI: 0.680–0.761) was a better indicator to

12   predict different types of hypertension than BMI (AUC = 0.698; 95% CI:

13   0.658–0.737) ,WHR (AUC = 0.684; 95% CI: 0.643–0.726) and TG (AUC = 0.663;

14   95% CI: 0.620–0.706) in females; however, WC (AUC = 0.734 95% CI: 0.700–0.769)

15   performed better than BMI (AUC = 0.707, 95% CI: 0.672–0.742), WHR (AUC =

16   0.688; 95% CI: 0.650–0.725), LAP (AUC = 0.677; 95% CI: 0.640–0.713) and TG

17   (AUC = 0.607; 95% CI: 0.568–0.646) in males. The best cut-off values of LAP to

18   predict hypertension were 63.892 in males and 30.860 in females.

19   **Interaction effects between LAP and family history of hypertension**

20   The interaction effects between LAP and family history of hypertension are presented

21   in Table 5. Significant interaction effects between LAP and family history of

22   hypertension were observed in males. The results of RERI (1.652; 95% CI:

23   0.267–3.037) and AP (0.516; 95% CI: 0.238–0.794) indicated a significant interaction

24   effect of family history of hypertension and LAP on hypertension, but the result of SI

25   (3.998; 95% CI: 0.897–17.820) did not.

26   However, no statistically significant interaction effects were found between LAP

27   and family history of hypertension in females, as indicated by all the three indicators.

28   RERI was - 0.673 (95% CI: -2.566–1.220); AP was -0.328 (95% CI: -1.451–0.795);

1 and SI was 0.610 (95% CI: 0.125–2.979).

2 **Discussion**

3 With the rapid development of the economy and sedentary lifestyle, elevated blood

4 pressure has become a common and serious public health issue.[31] The prevalence of

5 prehypertension and hypertension has significantly increased.[32] Elevated blood

6 pressure is caused by diverse factors, among which obesity is closely related to

7 hypertension.[33] An increase in body weight is typically followed by enhanced blood

8 pressure.[12] Extensive studies have found that obesity, especially visceral adipose

9 tissue, could strongly increase the blood pressure.[33]

10 The mechanisms underlying the interaction between obesity and hypertension are

11 complicated. The mechanisms of obesity-induced hypertension include sodium

12 retention, insulin resistance, activation of renin-angiotensin-aldosterone, altered

13 vascular function, and secretion of relevant adipokines.[34] In addition, the mechanisms

14 of blood pressure increase can be activated by visceral fat.[35]

15 Substantial evidences proved that the harm of the fat accumulation was greater than

16 the total amount of fat.[36, 37] However, traditional obesity indexes, such as BMI, WC,

17 and WHR, have some limitations when distinguishing between subcutaneous fat and

18 visceral fat. Therefore, a new obesity index that can predict visceral fat easily and

19 effectively is urgently needed. After Kahn first demonstrated that LAP performs

20 better than BMI for recognizing the cardiovascular risk, domestic and foreign scholars

21 have paid increasing attention to LAP. LAP, a combination of WC and TG, is an

22 accessible and inexpensive way to assess visceral fat.[13] It is a well-known fact that TG

23 can reflect the degree of visceral fat accumulation and WC is strongly associated with

24 hypertension.[12] Notably, hypertriglyceridemic waist (HTGW) is also calculated based

25 on the combination of TG and WC. However, LAP, a continuous indicator, is superior

26 to reflect visceral fat than HTGW,[38] a discontinuous indicator.[21] Therefore, LAP was

27 used as a visceral obesity indicator in this study.

28 LAP based on the hypothesis of minimum waist circumference includes the rachis,

12

1 abdominal viscera and muscle.[13] Therefore, the differences between the actual WC

2 and the minimum WC can represent abdominal adipose tissue.[13] Notably, LAP in

3 almost all studies is calculated by data obtained based on the third National Health

4 and Nutrition Examination Survey in the United States.[13] Because of differences in

5 race, dietary habits, or lifestyle, individuals from different countries should have

6 different visceral adipose tissues. It has been demonstrated that there are considerable

7 differences in visceral adipose tissues between Chinese individuals and Europeans or

8 Americans.[39] Therefore, LAP was calculated in our study using a modified formula so

9 that it could apply to the individuals dwelling in Southern China.

10 As expected, a significant association was found between LAP and hypertension in

11 the present study. Our findings are consistent with those in studies by Zhong et al,[17]

12 Song et al,[37] and Shen et al,[22] all of which have demonstrated that LAP is an effective

13 and reliable diagnostic indicator of hypertension. Participants with significantly

14 higher LAP had higher risks of prehypertension and hypertension than those with

15 lower LAP. Multinomial logistic regression analysis revealed that after adjusting for

16 other factors, the risks of prehypertension and hypertension in the group with the

17 highest LAP level were 2.10 and 3.15 times higher in females, respectively, than

18 those in the group with the lowest LAP.

19 Wang et al.found LAP is a better index to predict the risk of hypertension.[40]

20 However, Gao et al found that the performance of LAP was superior to that of BMI in

21 male Mongolians;[23] this findings may be due to the apparently lower prevalence of

22 high TG in female Mongolians than in male Mongolians (13.20% vs 23.10%，$P <$

23 0.05), and the facts might disturb the association between LAP and hypertension in

24 female Mongolians. Several study found the superiority of LAP over BMI for

25 detection of hypertension and prehypertension in both genders.[21,37,40] However, in the

26 present study, we also found that LAP perform better than BMI in female. According

27 to Kahn,[41] the annual LAP changes were reduced at older age in male. Advancing age

28 is associated with a progressive increase in systolic BP levels and with development

29 and progression of arterial hypertension because of a number of factors, including

atherosclerotic changes, large artery stiffening, altered renal function, and arterial baroreflex impairmen,[42] That is to say, increase in blood pressure was thought to be an unavoidable consequence of aging. Thus, the superiority of LAP for predicting hypertension in male may be disturbed by the larger-scale proportion of elder man (23.7%) in our study. In our study, LAP perform better in predicting the hypertension risk than TG in both sex. However, due to low predictive value of TG in southern China, LAP which combines of TG and WC is slightly inferior to WC.

In general, LAP, which applied to the Southern Chinese population, was a better indicator for predicting the hypertension risk in females in this study. In addition, large studies have demonstrated that family history of hypertension is a critical risk factor for hypertension, and individuals with family history of hypertension are 2–4 times more likely to develop hypertension than those without the family history of hypertension.[43] The interaction analysis in this study indicates the synergistic effect of LAP and family history on the hypertension risk in males, but no statisitically significant differences in the interaction effect in females. In fact, cardiovascular events occur at a lower rate in females than in males.[44] In our study, the female participants who had both LAP and family history of hypertension were rarely observed and the prevalence rates of hypertension at a lower rate in females than in males no matter premenopausal status or menopausal status.[45] Our study suffer from a small sample size, especially in females. The fewer positive female observers which had higher LAP and family history of hypertension lead to no statistically significant differences in the interaction effect on the hypertension risk in females. The interaction in female was not statistically significant, but their synergistic effect was obvious. The synergistic effect between family history of hypertension and LAP on the hypertension risk was demonstrated in our study as well as in other studies.[21, 40] Visceral obesity and family history of hypertension may result in increased blood pressure through some unknown mechanisms. However, further studies are needed to investigate the interaction effect between LAP and family history of hypertension on the hypertension risk.

14

To date, LAP is an inexpensive screening tool to identify visceral adipose tissue, and the method has high reproducibility. LAP, which was proposed by Kahn, was developed for the Western population. Thus this study explored the validity of LAP, which was calculated based on the Southern China population. The findings suggest LAP might perform better in predicting the hypertension risk than BMI, WHR and TG in Southern Chinese females.

This study has some limitations. First of all, because this is a cross-sectional study, the present results are not sufficient to indicate causality. Secondly, the population of our study can partially represent the general population in the Southern China, but can not fully represent this region. Furthermore, this article is lack of adjustment for renal function, and other risk factors for hypertension (such as serum uric acid). Finally, because of the small sample size in this study, further studies with a larger sample size are needed to investigate whether the modified LAP applies to all the residents dwelling in Southern China.

CONCLUSION

In conclusion, LAP was significantly associated with the hypertension risk, and higher LAP levels had relatively higher blood pressure. LAP performed better in predicting hypertension than did BMI, WHR and TG in the Southern China female population. The synergistic effect of LAP and family history of hypertension was demonstrated..

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Contributors

Jun-Xuan Huang, Pei-Xi Wang and Jin-Xiang Ma conceived and designed the study. Jun-Xuan Huang, Xin-Yu Bao, Yi-Xian Xie, Xiao-Xia Zhang, Xin Peng, Yan Liu and Meng-Jiao Cheng contributed to collection of the data, analyzed the data and interpretation of the results. Jun-Xuan Huang wrote the draft manuscript. Jin-Xiang

Ma, Pei-Xi Wang and Jun-Xuan Huang finalized the manuscript with inputs from all authors. All of the authors approved the final version submitted for publication.

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Competing interests

The authors declared that they had no conflict of interest.

Ethics statement

This study was approved by the Ethics Committee of Guangzhou Medical University. Written informed consent was obtained from each study participant before investigation.

Data sharing statement

Our data might not be shared directly, because it's our team work and the data belongs

to our team.Thus consent should be attained from team members.

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The titles and legends of figure

Title

Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

Title

Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

1 **Table 1** Basic characteristics of the participants

Variables	Normotension (N = 832)	Prehypertension (N = 789)	Hypertension (N = 458)	χ^2 / Z	*P*-value
Sex (%)				135.625	< 0.001
Male	32.57	58.68	58.52		
Female	67.43	41.32	41.48		
Age (years)	36.42 ± 10.59	41.38 ± 12.71	48.93 ± 12.75	267.206	< 0.001
Marital status (%)				21.287	< 0.001
Currently not married	23.20	18.76	12.66		
Currently married	76.80	81.24	87.34		
Education level (%)				101.355	< 0.001
Elementary school and lower	15.87	21.55	36.46		
Secondary school	36.30	38.53	39.96		
Senior high school and higher	47.83	39.92	23.58		
Physical activity (%)				2.688	0.611

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Seldom or never	35.70	34.22	31.22		
Moderate	17.43	18.25	18.78		
High	46.87	47.53	50.00		
Smoker (%)				50.346	< 0.001
Non-smoker	82.25	71.61	67.90		
Smoker	16.18	26.87	28.61		
Former smoker	0.97	1.52	3.49		
Drinker (%)				30.865	< 0.001
Non-drinker	84.11	76.34	72.53		
Drinker	14.91	22.39	24.62		
Former drinker	0.98	1.27	2.85		
BMI				255.012	< 0.001
< 18.5	13.70	5.20	2.18		
18.5–23.9	68.51	54.88	41.70		
24–27.9	14.30	31.69	37.55		

≥ 28	3.49	8.24	18.56		
WC	75.61±8.19	81.61±9.04	87.02±9.95	411.441	< 0.001
WHR	0.85± 0.06	0.88± 0.07	0.91± 0.06	248.475	< 0.001
Fasting plasma glucose (mmol/L)	4.69 ± 0.82	4.98 ± 1.33	5.31 ± 1.86	90.399	< 0.001
Total cholesterol (mmol/L)	4.70 ± 0.96	4.98 ± 1.07	5.26 ± 1.15	88.325	< 0.001
Triglyceride (mmol/L)	1.26 ± 0.83	1.77 ± 1.77	2.15 ± 2.25	178.995	< 0.001
Systolic blood pressure (mmHg)	107.97 ± 7.80	125.45 ± 6.65	144.78 ± 18.55	1533.137	< 0.001
Diastolic blood pressure (mmHg)	69.49 ± 6.40	79.59 ± 5.99	91.49 ± 11.33	1206.505	< 0.001
Family history of hypertension (%)				18.391	0.005
Only father	11.42	11.03	11.14		
Only mother	12.02	15.08	17.25		
Both parents	5.41	4.82	8.95		
Neither	71.15	69.07	62.66		
LAP	29.14 ± 27.00	52.15 ± 63.50	75.87 ± 99.81	355.133	< 0.001

1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

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Table 2 Comparison of blood pressure among four quartiles of LAP

Variables	LAP				Z	P-value
	Q1	Q2	Q3	Q4		
Male						
Systolic blood pressure (mmHg)	119.33 ± 13.72	125.61 ± 14.86	129.23 ± 16.38	133.36 ± 17.85	106.793	< 0.001
Diastolic blood pressure (mmHg)	75.84 ± 9.89	80.55 ± 9.84	82.56 ± 10.74	85.64 ± 11.36	106.285	< 0.001
Female						
Systolic blood pressure (mmHg)	110.45 ± 13.91	114.95 ± 15.07	119.66 ± 15.91	130.25 ± 19.78	184.926	< 0.001
Diastolic blood pressure (mmHg)	71.05 ± 9.45	73.29 ± 9.60	76.21 ± 9.96	81.04 ± 11.70	134.730	< 0.001

Table 3 Multinomial logistic regression analysis of LAP associated with hypertension status

	OR[a](95% CI)		OR[b](95% CI)		OR[c](95% CI)	
Quartiles of LAP	prehypertension	hypertension	prehypertension	hypertension	prehypertension	hypertension
Male						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）

Q2	2.98***	4.70***	2.22***	2.38**	1.73*	1.61
	(1.88, 4.72)	(2.34, 9.45)	(1.48, 3.34)	(1.36, 4.16)	(1.12, 2.67)	(0.89, 2.94)
Q3	4.48***	8.26***	2.68***	3.90***	1.66*	1.75
	(2.85, 7.03)	(4.21, 16.21)	(1.74, 4.12)	(2.24, 6.82)	(1.03, 2.68)	(0.94, 3.26)
Q4	4.65***	17.82***	3.14***	9.02***	1.67	2.79***
	(2.93, 7.36)	(9.21, 34.46)	(1.95, 5.07)	(5.11, 15.93)	(0.96, 2.92)	(1.43, 5.44)
Female						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	1.75**	2.19**	1.046	1.19	0.91	1.015
	(1.22, 2.51)	(1.27, 3.77)	(0.69,1.58)	(0.62,2.29)	(0.59,1.41)	(0.51,2.03)
Q3	3.35***	6.50***	1.68**	1.87	1.31	1.19
	(2.27, 4.93)	(3.83, 11.02)	(1.11,2.52)	(0.99,3.49)	(0.84,2.05)	(0.60,2.38)
Q4	5.99***	20.06***	3.26***	6.32***	2.10**	3.15***
	(3.74, 9.59)	(11.37, 35.38)	(2.09,5.10)	(3.42,11.65)	(1.26,3.51)	(1.56,6.39)

1   OR=Odds ratio; CI=confidence interval; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

2   [a], unadjusted.

3   [b], adjusted for age, sex, marital status, educational level

1   ^c, adjusted for physical activity, smoker, drinker, BMI, WHR, fasting plasma glucose, family history of hypertension, and all the factors in b.
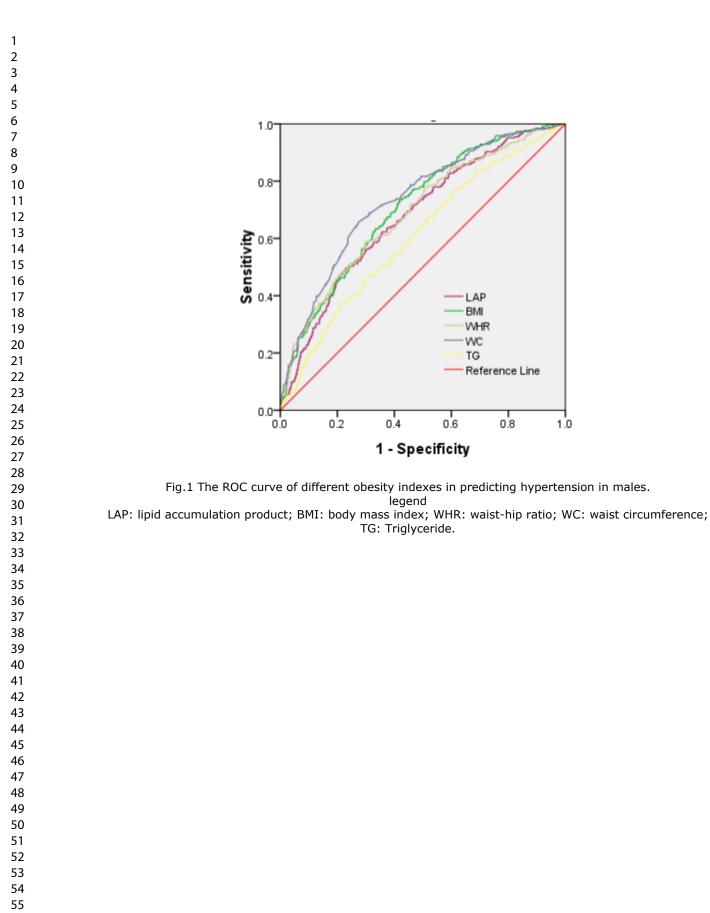
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3   **Table 4** Predicting hypertension by different obesity indexes

Variables	Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index	AUC(95% CI)	*P*-value
Male						
BMI	23.004	73.51	58.08	0.316	0.707 (0.672, 0.742)	< 0.001
WHR	0.906	58.58	70.27	0.289	0.688 (0.650, 0.725)	< 0.001
LAP	63.892	49.63	76.99	0.266	0.677 (0.640, 0.713)	< 0.001
WC	85.05	65.67	72.60	0.383	0.734 (0.700, 0.769)	< 0.001
TG	1.91	46.27	70.14	0.164	0.607 (0.568, 0.646)	< 0.001
Female						
BMI	21.767	81.58	50.73	0.323	0.698 (0.658, 0.737)	< 0.001
WHR	0.860	74.21	55.24	0.294	0.684 (0.643, 0.726)	< 0.001
LAP	30.860	68.95	67.42	0.363	0.721 (0.680, 0.761)	< 0.001
WC	79.90	72.11	64.94	0.370	0.725 (0.686, 0.766)	< 0.001

	TG	1.26	63.68	64.49	0.282	0.663 (0.620, 0.706)	< 0.001

1 BMI: body mass index; WHR: waist-hip rate; LAP: lipid accumulation product; WC: waist circumference; TG: Triglyceride; AUC: area under curve;

2 OR=Odds ratio; CI=confidence interval.

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4 **Table 5** Interaction effects between LAP and family history of hypertension

Variables	Variables	N	OR^c (95% CI)	Interaction indexes (95% CI)
Male				
LAP^a	Family history^b			
-	-	486	1 (reference)	RERI = 1.652 (0.267, 3.037)*
-	+	215	1.189 (0.772, 1.832)	AP = 0.516 (0.238, 0.794)*
+	-	173	1.362 (0.875, 2.121)	SI = 3.998 (0.897, 17.820)
+	+	128	3.203*** (2.002, 5.124)	
Female				
LAP^a	Family history^b			
-	-	657	1 (reference)	RERI = -0.673 (-2.566, 1.220)

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-	+	276	1.995** (1.284, 3.099)	AP = -0.328 (-1.451, 0.795)
+	-	108	1.729*(1.023, 2.922)	SI = 0.610 (0.125, 2.979)
+	+	36	2.051 (0.919, 4.589)	

1   LAP: lipid accumulation production; RERI: relative excess risk of interaction ; AP: attributable proportion due to interaction; SI: synergy index; OR=Odds

2 ratio; CI=confidence interval; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

3   [a], grouped by the cut-off values in Table 4.

4   [b], family history of hypertension was defined as one parent or both parents having hypertension.

5   [c], adjusted for age, marital status, educational level, physical activity, smoker, drinker, BMI, and WHR.

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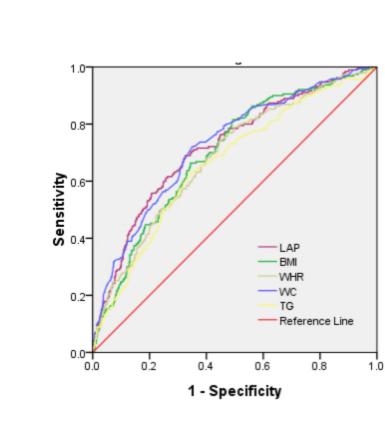41
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Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.
legend
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference;
TG: Triglyceride.

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Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.
legend
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference;
TG: Triglyceride.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 3
Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7-8
		(*c*) Explain how missing data were addressed	Page 5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8-9; Table 1
		(b) Give reasons for non-participation at each stage	Not application
		(c) Consider use of a flow diagram	Not application
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Not application
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8-9; Table 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-10; Table 3; Table 5
		(b) Report category boundaries when continuous variables were categorized	Page 6-8; Table 1; Table 2 ; Table 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not application
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11; Table 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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Keywords:	Hypertension < CARDIOLOGY, LAP, Family history, Interaction effect

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1 **Interaction of lipid accumulation product and family history of hypertension on**

2 **hypertension risk: A cross-sectional study in the Southern Chinese population**

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ABSTRACT

Objectives: This study aimed at investigating the applicability of a novel index based on waist circumference (WC) and Triglyceride (TG) which was named lipid accumulation product (LAP) in the Southern Chinese population, and compared the predictive effects of LAP and other obesity indicators on hypertension risk. Moreover, this study investigated the interactive effects of LAP and family history of hypertension.

Methods: A total number of 2079 of community-dwelling adults in Southern China were enrolled in this cross-sectional study. The participants underwent questionnaire surveys, anthropometric tests, and laboratory examinations. The multivariate logistic regression model and receiver operating characteristic (ROC) curves, including LAP, body mass index (BMI), waist-hip ratio (WHR), WC,and TG were used to assess the association between hypertension risk and obesity indexes. The interaction effects were evaluated by relative excess risk of interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI).

Results: Higher LAP levels have a relatively higher risk of having hypertension in both sexes (males: adjusted odds ratio [OR] = 2.79 per SD increase, 95% confidence interval [CI] = 1.43-5.44, $P < 0.001$; females: adjusted OR:3.15,95%CI=1.56-6.39, $P < 0.001$). LAP (area under curve [AUC] = 0.721; 95% CI: 0.680–0.761) is a better indicator in identifying hypertension risk than BMI, WHR, and TG in females, but WC performed better in males. A significant interaction between LAP and family history of hypertension was observed in males (RERI = 1.652, 95% CI: 0.267–3.037; AP = 0.516, 95% CI: 0.238–0.794; SI = 3.998, 95% CI: 0.897–17.820), but there is no statistically significant differences in females.

Conclusions: LAP significantly associated with hypertension risk in the Southern Chinese population. It has better performance than BMI, WHR, and TG on predicting hypertension risk of the Southern Chinese female population. This demonstrated the synergistic effect between LAP and family history of hypertension.

1 **Keywords: Hypertension, LAP, Family history, Interaction effect**

2 **Strengths and limitations of this study**

3 **Strengths**:

4 1. Our study is the first to examine the validity of LAP, which was calculated using a

5 modified formula, in the Southern China population.

6 **Limitations:**

7 1. This is a cross-sectional study; the results are not sufficient to indicate causality.

8 2. The population of our study can partially represent the general population in the

9 Southern China but cannot fully represent this region.

10 3. Lack of the adjustment for renal function, and other risk factors for hypertension

11 (such as serum uric acid) in our study.

12 4. This study has small sample size, so further studies with a larger sample size are

13 needed to investigate whether the modified LAP applies to all the residents dwelling

14 in Southern China.

4

1   **INTRODUCTION**

2   Hypertension, a significant risk factor of cardiovascular disease,[1] is one of the most

3   prevalent public health problems in the world and is the leading contributor to the

4   global burden of disease and mortality. Nowadays, the number of adults with

5   hypertension in the world is being predicted to increase by about 60% to a total of

6   1.56 billion in 2025, and one-third of adults are suffering from hypertension in

7   China.[2, 3]

8   Obesity, especially visceral fat, and family history of hypertension contributes to

9   hypertension significantly.[4-6] Numerous studies agree on the idea that people with

10 hypertension's family history have higher chance to get hypertension.[6-9] Usually,

11 when it comes to obesity, the indexes that are most frequently used to assess obesity

12 are body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR);

13 however, these traditional obesity indexes merely reflect the degrees of overweight

14 and abdominal obesity, also, cannot distinguish the difference between subcutaneous

15 fat and visceral fat.[10] Micromagnetic resonance imaging and microcomputed

16 tomography, which are the visceral fat golden standard measurement methods,is

17 inconvenient and expensive.[11] Moreover, they are not suitable for large-scale

18 epidemiological investigations. Therefore, it is necessary to discover a new obesity

19 indicator that can predict visceral fat from subcutaneous fat more conveniently and

20 economically.

21 Recently, increasing attention has been directed towards lipid accumulation product

22 (LAP). LAP, a new obesity index computed from WC and triglyceride (TG), is a

23 useful indicator of visceral fat,[12] as demonstrated by Kahn in 2005[13]. Some studies

24 suggest that LAP can also be used to identify metabolic syndromes,[14, 15] type 2

25 diabetes mellitus,[16] stroke,[17] and arterial stiffness.[18] Additionally, several

26 cross-sectional studies conducted in Japan,[19] India,[14] and Brazil indicate that LAP

27 significantly associated with cardiovascular disease and is a better indicator than BMI

28 for identifying cardiovascular risk.[13, 20] A few national studies have investigated the

29 association between LAP and hypertension in China, and all of them were conducted

in northern China, including Bengbu,[21] Beijing,[22] and Inner Mongolia.[23] With a vast territory, China has a tremendous difference between South and North. Due to the geographical environment and dietary habits that have formed throughout its long history, there are some dietary and cultural differences between Northern and Southern China.[24] The Northern region shows a high intake of wheat, tubers, and liquor, etc. While southerner has a high intake of rice, vegetables, meat, poultry, fish etc.[24] The Carbohydrate-rich pattern of the northern region is associated with a high risk of hypertriglyceridemia and higher BMI. Meanwhile, significant differences are found in systolic blood pressure (SBP)/diastolic blood pressure (DBP) between southern Chinese and northern Chinese owing to different climate and dietary habits between southern and northern.[25] Studies have found that the northerners were heavier and had higher triglycerides level than southerners.[26, 27] Differences in dietary habits, or lifestyle, individuals from different regions should lead to different LAP. LAP has a different situation in the north and south. Thus, the applicability of LAP in predicting hypertension in Southern China is worth studying. However, rare studies have compared LAP with other obesity indexes in the Southern Chinese population. Besides, almost all studies about LAP used the formula that was developed based on the third National Health and Nutrition Examination Survey in the US. Therefore, it is reasonable to suggest that the calculation formula of LAP needs to be modified in the Chinese population.

To the best of our knowledge, no studies have attempted to adjust the calculation formula of LAP so that it can apply to the Southern Chinese population, and rare studies have explored additive interactions between family history of hypertension and LAP. Thus, the primary purpose of this study was to investigate the applicability of LAP in the Southern Chinese population and compare the predictive effects of LAP and other obesity indicators on hypertension risk. And the secondary purpose of the study was to assess interactive effects between LAP and family history of hypertension to predict the hypertension risk in the Southern Chinese population.

METHODS

6

Study design and subjects

A cross-sectional survey based on community health was conducted in the Foshan city of Guangdong province in Southern China. Recruiting the enrollers took place on March 2017. The study samples were selected by a multistage and stratified random sampling method. The stratification according to the economic levels and randomly selected street communities at economic levels, then randomly selected communities in street communities according to proportion. Communities residents were then randomly selected from the household lists. A total of 3760 individuals were enrolled in this study; among them, 1681 participants who lacked complete data on demographic characteristics, anthropometric tests, or laboratory examinations were excluded. There are no statistically significant differences in age and sex between excluded participants and included participants. Finally, 2079 adults who had complete data were included in the analysis.

Patient and public involvement

Patients or public were not involved in this study.

Ethics statement

This study was approved by the Ethics Committee of Guangzhou Medical University. Written informed consent was obtained from each study participant before investigation.

General study questionnaire

An interview-based survey was performed using a questionnaire by trained staff. Socio-demographic data, family history of hypertension, cigarette smoking, and alcohol drinking were investigated. Smokers were defined as the participants smoking at least 1 cigarette/day for at least 6 months. Drinkers were defined as individuals consuming at least 30 ml alcohol/week for 1 year or more. Physical activities were divided into "insufficiently active" and "sufficiently active." Participants with "insufficiently active" were defined as those who performed activity less than 150min/week. Participants with "sufficiently active" were defined as those who

exercised more than 150min/week.[28] Marital status was classified as "currently not married" and "currently married"; "married" was regarded as "currently married," and "divorced/widowed/single" was regarded as "currently not married." Educational level was categorized as "elementary school or lower," "secondary school," and "senior high school or higher."

Anthropometric tests and laboratory examinations

The participants were required to take off their shoes and wear lightweight clothing for weight and height measurements. WC was measured at the level of 1 cm above the navel.[29] Automatic sphygmomanometer (OMRON, hem-7125) was used to measure blood pressure (BP) of participants. BP measurement was conducted thrice in a quiet environment, and the participants rested at least one minute between each time of measurement. The mean of the three measurements was used in the analysis. Prehypertension was defined as SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, and hypertension was defined as SBP of $\geq$ 140 mmHg, DBP of $\geq$ 90 mmHg, and/or a reported medical history of anti-hypertensive medication.[29] The BMI was calculated as weight in kilograms divided by the square of the height in meters. Overweight was defined as BMI of 24–27.9 kg/m^2, and obesity was defined as BMI of $\geq$ 28 kg/m^2. The fasting blood samples were collected from the participants in the morning after an overnight fast and were used to assess fasting plasma glucose, total cholesterol, and TG levels.

According to Kahn's theory,[13] LAP is calculated as [WC (cm) - The minimum of WC (male)] $\times$ [TG (mmol/L)] for males and [WC (cm) - The minimum of WC (female)] $\times$ [TG (mmol/L)] for females, and the minimum waist size theoretically contains only the abdomen, muscle, viscera, and vertebral bone.[13] Visceral fat can be estimated by the difference between the WC and the minimum waist size. In the present study, the WC of the studied population was skewed; therefore, the WC was log-transformed. The minimum WC was estimated by the mean WC minus two standard deviations after log-transformation in the local participants aged 18–24 years.[13, 22]

Statistical analyses

According to the hypertension status, the enrollees were divided into three groups (normotension, prehypertension, and hypertension). The frequency (%) was used to describe sex, marital status, education level, physical activity, BMI, smoker, and drinker. Mean ± standard deviation (SDs) was used to describe the WC, WHR, fasting plasma glucose, total cholesterol, TG, SBP, DBP, and LAP. LAP was divided into four groups by the quartiles, i.e., Q1, Q2, Q3, and Q4. The differences of quantitative data across different hypertension statuses were analyzed by the Kruskal-Wallis H test because the data had skewed distribution. Categorical variables were analyzed by the Chi-squared test. The multivariate logistic regression model was used to analyze the relationship between LAP and risk factors of hypertension and prehypertension. The receiver operating characteristics (ROC) curves were applied to identify the superior obesity index and the best cut-off value of LAP to predict the hypertension risk. Moreover, the interaction effects between LAP and family history of hypertension were assessed by some relevant indicators, including the relative excess risk of interaction ($RERI = OR_{11} - OR_{10} - OR_{01} + 1$), the attributable proportion due to interaction ($AP = [OR_{11} - OR_{10} - OR_{01} + 1]/OR_{11}$), and the synergy index ($SI = [OR_{11} - 1]/[OR_{01} - 1] + [OR_{10} - 1]$). If the interaction effect was not observed, the confidence interval of RERI and AP contained 0 and the confidence interval of S included 1.[30] The above indicators were calculated using an Excel table designed by Andersson et al.[30] All reported *P*-values were two-tailed, and a *P*-value of < 0.05 was considered significant. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

LAP

According to Kahn's theory,[13] LAP was calculated as (WC - 60.6) × (TG [mmol/L]) in males and (WC - 54.1) × (TG [mmol/L]) in females based on the actual data obtained from the Southern Chinese population.[22]

Basic characteristics of the study participants

A total number of 2079 of adults with an average age of 41.06 years were enrolled in the present study, including 1002 males (48.29%) and 1077 females (51.80%). The overall prevalence rates of normotension, prehypertension, and hypertension were 40.02%, 37.95%, and 22.03%, respectively. Male participants had a high prevalence of prehypertension and hypertension than female participants ($P < 0.001$). Statistically significant differences in age ($P < 0.001$), marital status ($P < 0.001$), education level ($P < 0.001$), smoker ($P < 0.001$), drinker ($P < 0.001$), and family history of hypertension ($P = 0.005$) were observed between normotension, prehypertension, and hypertension groups. However, no significant differences were observed in physical activity ($P = 0.550$) among the three groups. Anthropometric measurements found significant differences in BMI ($P < 0.001$), WC ($P < 0.001$), WHR ($P < 0.001$), LAP ($P < 0.001$) between the groups. Statistically significant differences found in laboratory examinations including fasting plasma glucose ($P < 0.001$), total cholesterol ($P < 0.001$), SBP ($P < 0.001$), and DBP ($P < 0.001$) between the groups (Table 1). And the basic characteristics of different sex of study participants were shown in table 2.

LAP and the risk factors of hypertension

In order to investigate the relationship between LAP and blood pressure, LAP was divided into four groups by quartile in different sex (Table 3). A significant association was observed between LAP and blood pressure in both male and female. The results in males and females showed that SBP ($P < 0.001$) and DBP ($P < 0.001$) were relatively elevated in participants with higher LAP levels.

Multinomial logistic regression analysis was conducted to evaluate the association between LAP quartiles and hypertension status (Table 4). Participants with the third and the fourth quartile of LAP were more likely to develop prehypertension and hypertension than those with the first quartile in both males and females.

After adjusting for age, marital status, and educational level, the risks of

1   prehypertension (adjusted OR: 3.14, 95% CI: 1.95–5.07) and hypertension (adjusted

2   OR: 9.02; 95% CI: 5.11–15.93) significantly increased in male participants with the

3   fourth quartile compared with those with the first quartile. For females, increasing

4   risks of prehypertension (adjusted OR: 3.26, 95% CI: 2.09–5.10) and hypertension

5   (adjusted OR: 6.32; 95% CI: 3.42–11.65) were observed in participants with the

6   fourth LAP quartile compared with those with the first one.

7   After controlling for age, marital status, educational level, physical activity,

8   smoking, alcohol consumption, BMI, WHR, fasting plasma glucose, and family

9   history of hypertension, the risks of prehypertension (adjusted OR: 1.67, 95% CI:

10 0.96–2.92) and hypertension (adjusted OR: 2.79, 95%CI: 1.43–5.44) significantly

11 increased in male participants with the fourth quartile compared with those with the

12 first quartile. Meanwhile, increasing risks of prehypertension (adjusted OR: 2.10, 95%

13 CI: 1.26–3.51) and hypertension (adjusted OR: 3.15, 95%CI: 1.56–6.39) were

14 observed in female participants with the fourth LAP quartile compared with those

15 with the first one.

16 The results of ROC curves analysis in males and females were shown in Figure. 1

17 and 2 and Table 5. LAP (AUC = 0.721; 95% CI: 0.680–0.761) was a better indicator

18 to predict different types of hypertension than BMI (AUC = 0.698; 95% CI:

19 0.658–0.737) ,WHR (AUC = 0.684; 95% CI: 0.643–0.726) and TG (AUC = 0.663;

20 95% CI: 0.620–0.706) in females; however, WC (AUC = 0.734 95% CI: 0.700–0.769)

21 performed better than BMI (AUC = 0.707, 95% CI: 0.672–0.742), WHR (AUC =

22 0.688; 95% CI: 0.650–0.725), LAP (AUC = 0.677; 95% CI: 0.640–0.713) and TG

23 (AUC = 0.607; 95% CI: 0.568–0.646) on males. The best cut-off values of LAP to

24 predict hypertension were 63.892 in males and 30.860 in females.

25 **Interaction effects between LAP and family history of hypertension**

26 The interaction effects between LAP and family history of hypertension are presented

27 in Table 6. Significant interaction effects between LAP and family history of

28 hypertension were observed in males. The results of RERI (1.652; 95% CI:

29 0.267–3.037) and AP (0.516; 95% CI: 0.238–0.794) indicated a significant interaction

1 effect of family history of hypertension and LAP on hypertension, but the result of SI

2 (3.998; 95% CI: 0.897–17.820) did not.

3   However, no statistically significant interaction effects were found between LAP

4 and family history of hypertension in females, which is indicated by all the three

5 indicators. RERI was - 0.673 (95% CI: -2.566–1.220); AP was -0.328 (95% CI:

6 -1.451–0.795); and SI was 0.610 (95% CI: 0.125–2.979).

7 **Discussion**

8 With the rapid development of the economy and sedentary lifestyle, elevated blood

9 pressure has become a common and serious public health issue.[31] The prevalence of

10 prehypertension and hypertension significantly increased.[32] Elevated blood pressure is

11 caused by diverse factors, among which obesity is closely related to hypertension.[33]

12 The prevalence of obesity increased by 13% in urban areas and by 85% in rural areas

13 in China, and more attention should thus be paid to this issue.[17] Extensive studies

14 found that obesity, especially visceral adipose tissue, could strongly increase the

15 blood pressure.[33]

16   The mechanisms underlying the interaction between obesity and hypertension are

17 complicated. The mechanisms of obesity-induced hypertension include sodium

18 retention, insulin resistance, activation of renin-angiotensin-aldosterone, altered

19 vascular function, and secretion of relevant adipokines.[34] Besides, the mechanisms of

20 blood pressure increase can be activated by visceral fat.[35]

21   Substantial evidence proved that the harm of the fat accumulation was greater than

22 the total amount of fat.[36, 37] However, traditional obesity indexes, such as BMI, WC,

23 and WHR, have limitations of distinguishing differences between subcutaneous fat

24 and visceral fat. Therefore, a new obesity index that can predict visceral fat easily and

25 effectively is urgently needed. After Kahn first demonstrated that LAP performs

26 better than BMI for recognizing the cardiovascular risk, domestic and foreign scholars

27 paid increasing attention to LAP. LAP, a combination of WC and TG, is an accessible

28 and inexpensive way to assess visceral fat.[13] It is a well-known fact that TG reflect the

12

degree of visceral fat accumulation and WC strongly associated with hypertension.[12] Notably, hypertriglyceridemic waist (HTGW) is also calculated based on the combination of TG and WC. However, LAP, as a continuous indicator, is superior to reflect visceral fat than HTGW,[38] a discontinuous indicator.[21] Therefore, LAP was used as a visceral obesity indicator in this study.

LAP is based on the hypothesis of minimum waist circumference includes the rachis, abdominal viscera and muscle.[13] Therefore, the differences between the actual WC and the minimum WC can represent abdominal adipose tissue.[13] Notably, LAP in almost all studies is calculated by data obtained based on the third National Health and Nutrition Examination Survey in the United States.[13] Because of differences in race, dietary habits, or lifestyle, individuals from different countries should have different visceral adipose tissues. It demonstrated that there are considerable differences in visceral adipose tissues between Chinese individuals and Europeans or Americans.[39] Therefore, LAP was calculated in our study using a modified formula so that it could apply to the individuals dwelling in Southern China.

As expected, a significant association was found between LAP and hypertension in the present study. Our findings are consistent with those in studies by Zhong et al,[17] Song et al,[37] and Shen et al,[22] all of which have demonstrated that LAP is an effective and reliable diagnostic indicator of hypertension. Participants with significantly higher LAP had higher risks of prehypertension and hypertension than those with lower LAP. Multinomial logistic regression analysis revealed that after adjusting for other factors, the risks of prehypertension and hypertension in the group with the highest LAP level were 2.10 and 3.15 times higher in females, respectively, than those in the group with the lowest LAP.

Wang et al.found LAP is a better index to predict the risk of hypertension.[40] However, Gao et al found that the performance of LAP was superior to that of BMI in male Mongolians;[23] this findings may be due to the apparently lower prevalence of high TG in female Mongolians than in male Mongolians (13.20% vs 23.10%，$P < 0.05$), and the facts might disturb the association between LAP and hypertension in

female Mongolians. Several studies found the superiority of LAP over BMI for detection of hypertension and prehypertension in both genders.[21, 37, 40] However, in the present study, we also found that LAP perform better than BMI in female. According to Kahn,[41] the annual LAP changes were reduced at older age in male. Advancing age is associated with a progressive increase in systolic BP levels and with development and progression of arterial hypertension because of a number of factors, including atherosclerotic changes, large artery stiffening, altered renal function, and arterial baroreflex impairmen,[42] That is to say, increase in blood pressure was thought to be an unavoidable consequence of aging. Thus, the superiority of LAP for predicting hypertension in male may be disturbed by the larger-scale proportion of elder man (23.7%) in our study. In our study, LAP perform better in predicting the hypertension risk than TG in both sex. However, due to low predictive value of TG in southern China, LAP which combines of TG and WC is slightly inferior to WC.

In general, LAP, which applied to the Southern Chinese population, was a better indicator for predicting the hypertension risk in females in this study. In addition, large studies have demonstrated that family history of hypertension is a critical risk factor for hypertension, and individuals with family history of hypertension are 2–4 times more likely to develop hypertension than those without the family history of hypertension.[43] The interaction analysis in this study indicates the synergistic effect of LAP and family history on the hypertension risk in males, but no statistically significant differences in the interaction effect in females. In fact, cardiovascular events occur at a lower rate in females than in males.[44] In our study, the female participants who had both LAP and family history of hypertension were rarely observed and the prevalence rates of hypertension at a lower rate in females than in males no matter premenopausal status or menopausal status.[45] Our study suffers from a small sample size, especially in females. The fewer positive female observers which had higher LAP and family history of hypertension lead to no statistically significant differences in the interaction effect on the hypertension risk in females. The interaction in female was not statistically significant, but their synergistic effect was

obvious. The synergistic effect between family history of hypertension and LAP on the hypertension risk was demonstrated in our study as well as in other studies.[21, 40] Visceral obesity and family history of hypertension may result in increased blood pressure through some unknown mechanisms. However, further studies are needed to investigate the interaction effect between LAP and family history of hypertension on the hypertension risk.

To date, LAP is an inexpensive screening tool to identify visceral adipose tissue, and the method has high reproducibility. LAP, which was proposed by Kahn, was developed for the Western population. Thus this study explored the validity of LAP, which was calculated based on the Southern China population. The findings suggest LAP might perform better in predicting the hypertension risk than BMI, WHR and TG in Southern Chinese females.

This study has some limitations. First of all, because this is a cross-sectional study, the present results are not sufficient to indicate causality. Secondly, the population of our study can partially represent the general population in the Southern China, but can not fully represent this region. Furthermore, this article is lack of adjustment for renal function, and other risk factors for hypertension (such as serum uric acid). Finally, because of the small sample size in this study, further studies with a larger sample size are needed to investigate whether the modified LAP applies to all the residents dwelling in Southern China.

CONCLUSION

In conclusion, LAP significantly associated with the hypertension risk, and higher LAP levels had relatively higher blood pressure. LAP performed better in predicting hypertension of the Southern China female population than BMI, WHR, and TG did. This demonstrated the synergistic effect of LAP and family history of hypertension.

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Contributors

Jun-Xuan Huang, Pei-Xi Wang and Jin-Xiang Ma conceived and designed the study. Jun-Xuan Huang, Xin-Yu Bao, Yi-Xian Xie, Xiao-Xia Zhang, Xin Peng, Yan Liu and Meng-Jiao Cheng contributed to collection of the data, analyzed the data and interpretation of the results. Jun-Xuan Huang wrote the draft manuscript. Jin-Xiang Ma, Pei-Xi Wang and Jun-Xuan Huang finalized the manuscript with inputs from all authors. All of the authors approved the final version submitted for publication.

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Competing interests

The authors declared that they had no conflict of interest.

Ethics statement

This study was approved by the Ethics Committee of Guangzhou Medical University. Written informed consent was obtained from each study participant before investigation.

Data sharing statement

Our data might not be shared directly, because it's our team work and the data belongs

to our team. Thus consent should be attained from team members.

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The titles and legends of figure

Title

Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

Title

Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

1   **Table 1** Basic characteristics of the participants

Variables	Normotension (N = 832)	Prehypertension (N = 789)	Hypertension (N = 458)	χ^2 / Z	*P*-value
Sex (%)				135.625	< 0.001
Male	32.57	58.68	58.52		
Female	67.43	41.32	41.48		
Age (years)	36.42 ± 10.59	41.38 ± 12.71	48.93 ± 12.75	267.206	< 0.001
Marital status (%)				21.287	< 0.001
Currently not married	23.20	18.76	12.66		
Currently married	76.80	81.24	87.34		
Education level (%)				101.355	< 0.001
Elementary school and lower	15.87	21.55	36.46		
Secondary school	36.30	38.53	39.96		
Senior high school and higher	47.83	39.92	23.58		
Physical activity (%)				2.688	0.611

22

Seldom or never	35.70	34.22	31.22		
Moderate	17.43	18.25	18.78		
High	46.87	47.53	50.00		
Smoker (%)				50.346	< 0.001
Non-smoker	82.25	71.61	67.90		
Smoker	16.18	26.87	28.61		
Former smoker	0.97	1.52	3.49		
Drinker (%)				30.865	< 0.001
Non-drinker	84.11	76.34	72.53		
Drinker	14.91	22.39	24.62		
Former drinker	0.98	1.27	2.85		
BMI				255.012	< 0.001
< 18.5	13.70	5.20	2.18		
18.5–23.9	68.51	54.88	41.70		
24–27.9	14.30	31.69	37.55		

≥ 28	3.49	8.24	18.56		
WC	75.61±8.19	81.61±9.04	87.02±9.95	411.441	< 0.001
WHR	0.85± 0.06	0.88± 0.07	0.91± 0.06	248.475	< 0.001
Fasting plasma glucose (mmol/L)	4.69 ± 0.82	4.98 ± 1.33	5.31 ± 1.86	90.399	< 0.001
Total cholesterol (mmol/L)	4.70 ± 0.96	4.98 ± 1.07	5.26 ± 1.15	88.325	< 0.001
Triglyceride (mmol/L)	1.26 ± 0.83	1.77 ± 1.77	2.15 ± 2.25	178.995	< 0.001
Systolic blood pressure (mmHg)	107.97 ± 7.80	125.45 ± 6.65	144.78 ± 18.55	1533.137	< 0.001
Diastolic blood pressure (mmHg)	69.49 ± 6.40	79.59 ± 5.99	91.49 ± 11.33	1206.505	< 0.001
Family history of hypertension (%)				18.391	0.005
Only father	11.42	11.03	11.14		
Only mother	12.02	15.08	17.25		
Both parents	5.41	4.82	8.95		
Neither	71.15	69.07	62.66		
LAP	29.14 ± 27.00	52.15 ± 63.50	75.87 ± 99.81	355.133	< 0.001

1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

1   **Table 2** Basic characteristics of the participants

Variables	Male					Female				
	Normotension (N = 271)	Prehypertension (N = 463)	Hypertension (N = 268)	χ^2 / Z	*P*-value	Normotension (N = 561)	Prehypertension (N = 326)	Hypertension (N = 190)	χ^2 / Z	*P*-value
Age (years)	36.57 ± 11.02	39.90 ± 12.37	47.15 ± 12.95	91.532	< 0.001	36.35 ± 10.39	43.48 ± 12.92	51.43 ± 12.11	201.378	< 0.001
Marital status (%)				26.019	< 0.001				7.928	0.019
Currently not married	31.37	22.46	13.06			19.25	13.50	12.11		
Currently married	68.63	77.54	86.94			80.75	86.50	87.89		
Education level (%)				24.179	< 0.001				116.258	< 0.001
Elementary school and lower	15.13	15.33	25.00			16.22	30.37	52.63		
Secondary school	37.64	40.39	45.15			35.65	35.89	32.63		
Senior high school and higher	47.23	44.28	29.85			48.13	33.74	14.74		
Physical activity (%)				0.807	0.668				2.979	0.226
insufficiently active	58.30	56.16	54.48			50.62	47.24	43.68		

sufficiently active	41.70	43.84	45.52			49.38	52.76	56.32		
Smoker (%)				7.037	0.132				5.893	0.122
Non-smoker	47.78	52.27	46.27			99.82	99.08	99.42		
Smoker	49.26	45.36	48.13			0.18	0.61	1.05		
Former smoker	2.96	2.38	5.60			0.00	0.31	0.53		
Drinker (%)				3.790	0.432				4.993	0.255
Non-drinker	60.74	61.47	57.30			95.62	97.53	94.15		
Drinker	36.67	36.36	38.20			4.20	2.47	5.32		
Former drinker	2.59	2.16	4.49			0.18	0.00	0.53		
BMI				148.700	< 0.001				99.205	< 0.001
< 18.5	16.61	4.54	1.49			12.30	6.13	3.16		
18.5–23.9	65.68	54.64	38.43			69.88	55.21	46.32		
24–27.9	14.39	33.26	39.18			14.26	29.45	35.26		
≥ 28	3.32	7.56	20.90			3.57	9.20	15.26		
WC	77.26±7.85	82.95±8.49	88.71±9.43	193.623	< 0.001	74.82±8.24	79.72±9.46	84.63±10.20	154.819	< 0.001

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WHR	0.86±0.06	0.89±0.06	0.92±0.06	126.195	< 0.001	0.84±0.07	0.86±0.07	0.89±0.06	183.524	< 0.001
Fasting plasma glucose (mmol/L)	4.76 ± 1.08	4.98 ± 1.38	5.30 ± 1.94	24.275	< 0.001	4.65 ± 0.66	4.99 ± 1.26	5.31 ± 1.75	71.169	< 0.001
Total cholesterol (mmol/L)	4.73 ± 1.00	4.98 ± 1.06	5.17 ± 1.25	20.500	< 0.001	4.69 ± 0.94	4.98 ± 1.08	5.39 ± 0.98	73.075	< 0.001
Triglyceride (mmol/L)	1.54 ± 1.08	1.93 ± 1.94	2.38 ± 2.68	40.974	< 0.001	1.12 ± 0.64	1.54 ± 1.47	1.82 ± 1.40	90.583	< 0.001
Systolic blood pressure (mmHg)	110.52 ± 6.13	125.60 ± 6.54	145.64 ± 17.04	706.430	< 0.001	106.73 ± 8.21	125.23 ± 6.81	143.57± 20.48	755.356	< 0.001
Diastolic blood pressure (mmHg)	70.82 ± 5.79	80.27 ± 5.75	93.11 ± 10.66	592.747	< 0.001	68.84 ± 6.59	78.63 ± 6.19	89.20 ± 11.87	553.348	< 0.001
Family history of hypertension (%)				16.427	0.012				6.847	0.335
Only father	10.70	11.23	13.81			11.76	10.74	7.37		
Only mother	11.44	17.28	18.28			12.30	11.96	15.79		
Both parents	6.27	4.75	9.70			4.99	4.91	7.89		
Neither	71.59	66.74	58.21			70.94	72.39	68.95		
LAP	38.69 ± 34.85	58.43 ± 65.52	87.83 ± 120.94	113.508	< 0.001	24.52 ± 20.75	43.24 ± 59.48	58.98 ± 54.19	159.320	< 0.001

1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

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6   **Table 3** Comparison of blood pressure among four quartiles of LAP

Variables	LAP				Z	*P*-value
	Q1	**Q2**	**Q3**	**Q4**		
Male						
Systolic blood pressure (mmHg)	119.33 ± 13.72	125.61 ± 14.86	129.23 ± 16.38	133.36 ± 17.85	106.793	< 0.001
Diastolic blood pressure (mmHg)	75.84 ± 9.89	80.55 ± 9.84	82.56 ± 10.74	85.64 ± 11.36	106.285	< 0.001
Female						
Systolic blood pressure (mmHg)	110.45 ± 13.91	114.95 ± 15.07	119.66 ± 15.91	130.25 ± 19.78	184.926	< 0.001
Diastolic blood pressure (mmHg)	71.05 ± 9.45	73.29 ± 9.60	76.21 ± 9.96	81.04 ± 11.70	134.730	< 0.001

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2   **Table 4** Multinomial logistic regression analysis of LAP associated with hypertension status

Quartiles of LAP	OR^a(95% CI)		OR^b(95% CI)		OR^c(95% CI)	
	prehypertension	hypertension	prehypertension	hypertension	prehypertension	hypertension
Male						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	2.98***	4.70***	2.22***	2.38**	1.73*	1.61
	(1.88, 4.72)	(2.34, 9.45)	(1.48, 3.34)	(1.36, 4.16)	(1.12, 2.67)	(0.89, 2.94)
Q3	4.48***	8.26***	2.68***	3.90***	1.66*	1.75
	(2.85, 7.03)	(4.21, 16.21)	(1.74, 4.12)	(2.24, 6.82)	(1.03, 2.68)	(0.94, 3.26)
Q4	4.65***	17.82***	3.14***	9.02***	1.67	2.79***
	(2.93, 7.36)	(9.21, 34.46)	(1.95, 5.07)	(5.11, 15.93)	(0.96, 2.92)	(1.43, 5.44)
Female						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	1.75**	2.19**	1.046	1.19	0.91	1.015
	(1.22, 2.51)	(1.27, 3.77)	(0.69,1.58)	(0.62,2.29)	(0.59,1.41)	(0.51,2.03)

	Q3	3.35***	6.50***	1.68**	1.87	1.31	1.19
		(2.27, 4.93)	(3.83, 11.02)	(1.11, 2.52)	(0.99, 3.49)	(0.84, 2.05)	(0.60, 2.38)
	Q4	5.99***	20.06***	3.26***	6.32***	2.10**	3.15***
		(3.74, 9.59)	(11.37, 35.38)	(2.09, 5.10)	(3.42, 11.65)	(1.26, 3.51)	(1.56, 6.39)

1   OR=Odds ratio; CI=confidence interval; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

2   [a], unadjusted.

3   [b], adjusted for age, sex, marital status, educational level

4   [c], adjusted for physical activity, smoker, drinker, BMI, WHR, fasting plasma glucose, family history of hypertension, and all the factors in b.

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6   **Table 5** Predicting hypertension by different obesity indexes

Variables	Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index	AUC(95% CI)	*P*-value
Male						
BMI	23.004	73.51	58.08	0.316	0.707 (0.672, 0.742)	< 0.001
WHR	0.906	58.58	70.27	0.289	0.688 (0.650, 0.725)	< 0.001
LAP	63.892	49.63	76.99	0.266	0.677 (0.640, 0.713)	< 0.001

WC	85.05	65.67	72.60	0.383	0.734 (0.700, 0.769)	< 0.001
TG	1.91	46.27	70.14	0.164	0.607 (0.568, 0.646)	< 0.001
Female						
BMI	21.767	81.58	50.73	0.323	0.698 (0.658, 0.737)	< 0.001
WHR	0.860	74.21	55.24	0.294	0.684 (0.643, 0.726)	< 0.001
LAP	30.860	68.95	67.42	0.363	0.721 (0.680, 0.761)	< 0.001
WC	79.90	72.11	64.94	0.370	0.725 (0.686, 0.766)	< 0.001
TG	1.26	63.68	64.49	0.282	0.663 (0.620, 0.706)	< 0.001

1   BMI: body mass index; WHR: waist-hip rate; LAP: lipid accumulation product; WC: waist circumference; TG: Triglyceride; AUC: area under curve;

2   OR=Odds ratio; CI=confidence interval.

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4   **Table 6** Interaction effects between LAP and family history of hypertension

Variables	Variables	N	OR[c] (95% CI)	Interaction indexes (95% CI)
Male				
LAP[a]	Family history[b]			

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-	-	486	1 (reference)	RERI = 1.652 (0.267, 3.037)[*]
-	+	215	1.189 (0.772, 1.832)	AP = 0.516 (0.238, 0.794)[*]
+	-	173	1.362 (0.875, 2.121)	SI = 3.998 (0.897, 17.820)
+	+	128	3.203[***] (2.002, 5.124)	

Female

LAP[a]	Family history[b]			
-	-	657	1 (reference)	RERI = -0.673 (-2.566, 1.220)
-	+	276	1.995[**] (1.284, 3.099)	AP = -0.328 (-1.451, 0.795)
+	-	108	1.729[*](1.023, 2.922)	SI = 0.610 (0.125, 2.979)
+	+	36	2.051 (0.919, 4.589)	

1   LAP: lipid accumulation production; RERI: relative excess risk of interaction ; AP: attributable proportion due to interaction; SI: synergy index; OR=Odds

2 ratio; CI=confidence interval; [***], $P < 0.001$; [**], $P < 0.01$; [*], $P < 0.05$.

3   [a], grouped by the cut-off values in Table 4.

4   [b], family history of hypertension was defined as one parent or both parents having hypertension.

5   [c], adjusted for age, marital status, educational level, physical activity, smoker, drinker, BMI, and WHR.

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Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.
legend
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference;
TG: Triglyceride.

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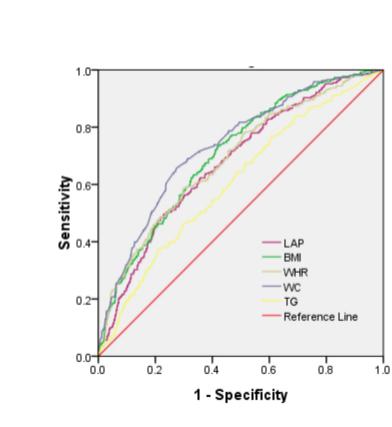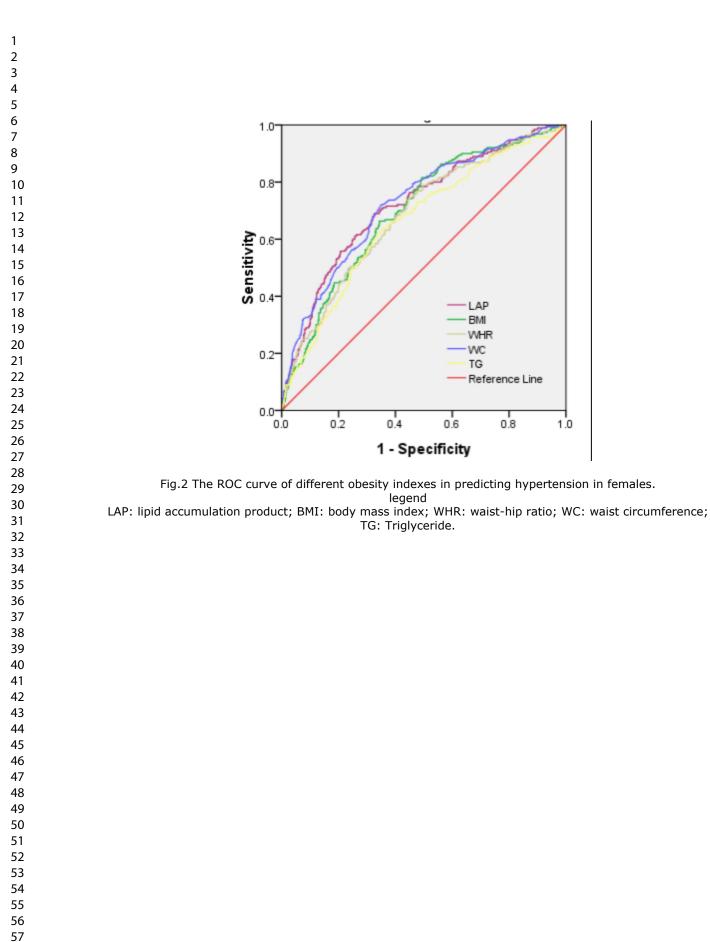51
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Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.
legend
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference;
TG: Triglyceride.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 3

Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7-8
		(*c*) Explain how missing data were addressed	Page 5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8-9; Table 1; Table 2
		(b) Give reasons for non-participation at each stage	Not application
		(c) Consider use of a flow diagram	Not application
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9; Table 1; Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Not application
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8-9; Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-10; Table 4; Table 6
		(*b*) Report category boundaries when continuous variables were categorized	Page 6-8; Table 1; Table 2; Table 3 ;

			Table 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not application
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11; Table 6
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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2

1 **ABSTRACT**

2 **Objectives:** This study aimed at investigating the applicability of a novel index based

3 on waist circumference (WC) and Triglyceride (TG) which was named lipid

4 accumulation product (LAP) in the Southern Chinese population, and compared the

5 predictive effects of LAP and other obesity indicators on hypertension risk. Moreover,

6 this study investigated the interactive effects of LAP and family history of

7 hypertension.

8 **Methods:** A total number of 2079 of community-dwelling adults in Southern China

9 were enrolled in this cross-sectional study. The participants underwent questionnaire

10 surveys, anthropometric tests, and laboratory examinations. The multivariate logistic

11 regression model and receiver operating characteristic (ROC) curves, including LAP,

12 body mass index (BMI), waist-hip ratio (WHR), WC, and TG were used to assess the

13 association between hypertension risk and obesity indexes. The interaction effects

14 were evaluated by relative excess risk of interaction (RERI), attributable proportion

15 due to interaction (AP), and synergy index (SI).

16 **Results:** Higher LAP levels have a relatively higher risk of having hypertension in

17 both sexes (males: adjusted odds ratio [OR] = 2.79 per SD increase, 95% confidence

18 interval [CI] = 1.43-5.44, $P < 0.001$; females: adjusted OR:3.15,95%CI=1.56-6.39, P

19 < 0.001). LAP (area under curve [AUC] = 0.721; 95% CI: 0.680–0.761) is a better

20 indicator in identifying hypertension risk than BMI, WHR, and TG in females, but

21 WC performed better in males. A significant interaction between LAP and family

22 history of hypertension was observed in males (RERI = 1.652, 95% CI: 0.267–3.037;

23 AP = 0.516, 95% CI: 0.238–0.794; SI = 3.998, 95% CI: 0.897–17.820), but there is no

24 statistically significant differences in females.

25 **Conclusions:** LAP significantly associated with hypertension risk in the Southern

26 Chinese population. It has better performance than BMI, WHR, and TG on predicting

27 hypertension risk of the Southern Chinese female population. Moreover, LAP and

28 family history of hypertension might synergistically increase the risk of hypertension.

1 **Keywords: Hypertension, LAP, Family history, Interaction effect**

2 **Strengths and limitations of this study**

3 **Strengths**:

4 1. Our study is the first to examine the validity of LAP, which was calculated using a

5 modified formula, in the Southern China population.

6 **Limitations:**

7 1. This is a cross-sectional study; the results are not sufficient to indicate causality.

8 2. The population of our study can partially represent the general population in the

9 Southern China but cannot fully represent this region.

10 3. Lack of the adjustment for renal function, and other risk factors for hypertension

11 (such as serum uric acid) in our study.

12 4. This study has small sample size, so further studies with a larger sample size are

13 needed to investigate whether the modified LAP applies to all the residents dwelling

14 in Southern China.

4

1 **INTRODUCTION**

2 Hypertension, a significant risk factor of cardiovascular disease,[1] is one of the most

3 prevalent public health problems in the world and is the leading contributor to the

4 global burden of disease and mortality. Nowadays, the number of adults with

5 hypertension in the world is being predicted to increase by about 60% to a total of

6 1.56 billion in 2025, and one-third of adults are suffering from hypertension in

7 China.[2, 3]

8 Obesity, especially visceral fat, and family history of hypertension contributes to

9 hypertension significantly.[4-6] Numerous studies agree on the idea that people with

10 hypertension's family history have higher chance to get hypertension.[6-9] Usually,

11 when it comes to obesity, the indexes that are most frequently used to assess obesity

12 are body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR);

13 however, these traditional obesity indexes merely reflect the degrees of overweight

14 and abdominal obesity, also, cannot distinguish the difference between subcutaneous

15 fat and visceral fat.[10] Micromagnetic resonance imaging and microcomputed

16 tomography, which are the visceral fat golden standard measurement methods,is

17 inconvenient and expensive.[11] Moreover, they are not suitable for large-scale

18 epidemiological investigations. Therefore, it is necessary to discover a new obesity

19 indicator that can predict visceral fat from subcutaneous fat more conveniently and

20 economically.

21 Recently, increasing attention has been directed towards lipid accumulation product

22 (LAP). LAP, a new obesity index computed from WC and triglyceride (TG), is a

23 useful indicator of visceral fat,[12] as demonstrated by Kahn in 2005[13]. Some studies

24 suggest that LAP can also be used to identify metabolic syndromes,[14, 15] type 2

25 diabetes mellitus,[16] stroke,[17] and arterial stiffness.[18] Additionally, several

26 cross-sectional studies conducted in Japan,[19] India,[14] and Brazil indicate that LAP

27 significantly associated with cardiovascular disease and is a better indicator than BMI

28 for identifying cardiovascular risk.[13, 20] A few national studies have investigated the

29 association between LAP and hypertension in China, and all of them were conducted

in northern China, including Bengbu,[21] Beijing,[22] and Inner Mongolia.[23] With a vast territory, China has a tremendous difference between South and North. Due to the geographical environment and dietary habits that have formed throughout its long history, there are some dietary and cultural differences between Northern and Southern China.[24] The Northern region shows a high intake of wheat, tubers, and liquor, etc. While southerner has a high intake of rice, vegetables, meat, poultry, fish etc.[24] The Carbohydrate-rich pattern of the northern region is associated with a high risk of hypertriglyceridemia and higher BMI. Meanwhile, significant differences are found in systolic blood pressure (SBP)/diastolic blood pressure (DBP) between southern Chinese and northern Chinese owing to different climate and dietary habits between southern and northern.[25] Studies have found that the northerners were heavier and had higher triglycerides level than southerners.[26, 27] Differences in dietary habits, or lifestyle, individuals from different regions should lead to different LAP. LAP has a different situation in the north and south. Thus, the applicability of LAP in predicting hypertension in Southern China is worth studying. However, rare studies have compared LAP with other obesity indexes in the Southern Chinese population. Besides, almost all studies about LAP used the formula that was developed based on the third National Health and Nutrition Examination Survey in the US. Therefore, it is reasonable to suggest that the calculation formula of LAP needs to be modified in the Chinese population.

To the best of our knowledge, no studies have attempted to adjust the calculation formula of LAP so that it can apply to the Southern Chinese population, and rare studies have explored additive interactions between family history of hypertension and LAP. Thus, the primary purpose of this study was to investigate the applicability of LAP in the Southern Chinese population and compare the predictive effects of LAP and other obesity indicators on hypertension risk. And the secondary purpose of the study was to assess interactive effects between LAP and family history of hypertension to predict the hypertension risk in the Southern Chinese population.

METHODS

6

1 **Study design and subjects**

2 A cross-sectional survey based on community health was conducted in the Foshan

3 city of Guangdong province in Southern China. Recruiting the enrollers took place on

4 March 2017. The study samples were selected by a multistage and stratified random

5 sampling method. The stratification according to the economic levels and randomly

6 selected street communities at economic levels, then randomly selected communities

7 in street communities according to proportion. Communities residents were then

8 randomly selected from the household lists. A total of 3760 individuals were enrolled

9 in this study; among them, 1681 participants who lacked complete data on

10 demographic characteristics, anthropometric tests, or laboratory examinations were

11 excluded. There are no statistically significant differences in age and sex between

12 excluded participants and included participants. Finally, 2079 adults who had

13 complete data were included in the analysis.

14 **Patient and public involvement**

15 Patients or public were not involved in this study.

16 **Ethics statement**

17 This study was approved by the Ethics Committee of Guangzhou Medical University.

18 Written informed consent was obtained from each study participant before

19 investigation.

20 **General study questionnaire**

21 An interview-based survey was performed using a questionnaire by trained staff.

22 Socio-demographic data, family history of hypertension, cigarette smoking, and

23 alcohol drinking were investigated. Smokers were defined as the participants smoking

24 at least 1 cigarette/day for at least 6 months. Drinkers were defined as individuals

25 consuming at least 30 ml alcohol/week for 1 year or more. Physical activities were

26 divided into "insufficiently active" and "sufficiently active." Participants with

27 "insufficiently active" were defined as those who performed activity less than

28 150min/week. Participants with "sufficiently active" were defined as those who

1 exercised more than 150min/week.[28] Marital status was classified as "currently not

2 married" and "currently married"; "married" was regarded as "currently married," and

3 "divorced/widowed/single" was regarded as "currently not married." Educational

4 level was categorized as "elementary school or lower," "secondary school," and

5 "senior high school or higher."

Anthropometric tests and laboratory examinations

7 The participants were required to take off their shoes and wear lightweight clothing

8 for weight and height measurements. WC was measured at the level of 1 cm above the

9 navel.[29] Automatic sphygmomanometer (OMRON, hem-7125) was used to measure

10 blood pressure (BP) of participants. BP measurement was conducted thrice in a quiet

11 environment, and the participants rested at least one minute between each time of

12 measurement. The mean of the three measurements was used in the analysis.

13 Prehypertension was defined as SBP of 120–139 mmHg and/or DBP of 80–89 mmHg,

14 and hypertension was defined as SBP of $\geq$ 140 mmHg, DBP of $\geq$ 90 mmHg, and/or a

15 reported medical history of anti-hypertensive medication.[29] The BMI was calculated

16 as weight in kilograms divided by the square of the height in meters. Overweight was

17 defined as BMI of 24–27.9 kg/m^2, and obesity was defined as BMI of $\geq$ 28 kg/m^2. The

18 fasting blood samples were collected from the participants in the morning after an

19 overnight fast and were used to assess fasting plasma glucose, total cholesterol, and

20 TG levels.

21 According to Kahn's theory,[13] LAP is calculated as [WC (cm) - The minimum of

22 WC (male)] $\times$ [TG (mmol/L)] for males and [WC (cm) - The minimum of WC

23 (female)] $\times$ [TG (mmol/L)] for females, and the minimum waist size theoretically

24 contains only the abdomen, muscle, viscera, and vertebral bone.[13] Visceral fat can be

25 estimated by the difference between the WC and the minimum waist size. In the

26 present study, the WC of the studied population was skewed; therefore, the WC was

27 log-transformed. The minimum WC was estimated by the mean WC minus two

28 standard deviations after log-transformation in the local participants aged 18–24

29 years.[13, 22]

1   **Statistical analyses**

2   According to the hypertension status, the enrollees were divided into three groups

3   (normotension, prehypertension, and hypertension). The frequency (%) was used to

4   describe sex, marital status, education level, physical activity, BMI, smoker, and

5   drinker. Mean ± standard deviation (SDs) was used to describe the WC, WHR, fasting

6   plasma glucose, total cholesterol, TG, SBP, DBP, and LAP. LAP was divided into

7   four groups by the quartiles, i.e., Q1, Q2, Q3, and Q4. The differences of quantitative

8   data across different hypertension statuses were analyzed by the Kruskal-Wallis H test

9   because the data had skewed distribution. Categorical variables were analyzed by the

10   Chi-squared test. The multivariate logistic regression model was used to analyze the

11   relationship between LAP and risk factors of hypertension and prehypertension. The

12   receiver operating characteristics (ROC) curves were applied to identify the superior

13   obesity index and the best cut-off value of LAP to predict the hypertension risk.

14   Moreover, the interaction effects between LAP and family history of hypertension

15   were assessed by some relevant indicators, including the relative excess risk of

16   interaction (RERI = OR_{11} - OR_{10} - OR_{01} + 1), the attributable proportion due to

17   interaction (AP = [OR_{11} - OR_{10} - OR_{01} + 1]/OR_{11}), and the synergy index (SI = [OR_{11} -

18   1]/[OR_{01} - 1] + [OR_{10} - 1]). If the interaction effect was not observed, the confidence

19   interval of RERI and AP contained 0 and the confidence interval of S included 1.[30]

20   The above indicators were calculated using an Excel table designed by Andersson et

21   al.[30] All reported *P*-values were two-tailed, and a *P*-value of < 0.05 was considered

22   significant. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc.,

23   Chicago, IL, USA).

24   **RESULTS**

25   **LAP**

26   According to Kahn's theory,[13] LAP was calculated as (WC - 60.6) × (TG [mmol/L])

27   in males and (WC - 54.1) × (TG [mmol/L]) in females based on the actual data

28   obtained from the Southern Chinese population.[22]

1   **Basic characteristics of the study participants**

2   A total number of 2079 of adults with an average age of 41.06 years were enrolled in

3   the present study, including 1002 males (48.29%) and 1077 females (51.80%). The

4   overall prevalence rates of normotension, prehypertension, and hypertension were

5   40.02%, 37.95%, and 22.03%, respectively. Male participants had a high prevalence

6   of prehypertension and hypertension than female participants ($P < 0.001$). Statistically

7   significant differences in age ($P < 0.001$), marital status ($P < 0.001$), education level

8   ($P < 0.001$), smoker ($P < 0.001$), drinker ($P < 0.001$), and family history of

9   hypertension ($P = 0.005$) were observed between normotension, prehypertension, and

10   hypertension groups. However, no significant differences were observed in physical

11   activity ($P = 0.550$) among the three groups. Anthropometric measurements found

12   significant differences in BMI ($P < 0.001$), WC ($P < 0.001$), WHR ($P < 0.001$), LAP

13   ($P < 0.001$) between the groups. Statistically significant differences found in

14   laboratory examinations including fasting plasma glucose ($P < 0.001$), total

15   cholesterol ($P < 0.001$), SBP ($P < 0.001$), and DBP ($P < 0.001$) between the groups

16   (Table 1). And the basic characteristics of different sex of study participants were

17   shown in table 2.

18   **LAP and the risk factors of hypertension**

19   In order to investigate the relationship between LAP and blood pressure, LAP was

20   divided into four groups by quartile in different sex (Table 3). A significant

21   association was observed between LAP and blood pressure in both male and female.

22   The results in males and females showed that SBP ($P < 0.001$) and DBP ($P < 0.001$)

23   were relatively elevated in participants with higher LAP levels.

24   Multinomial logistic regression analysis was conducted to evaluate the association

25   between LAP quartiles and hypertension status (Table 4). Participants with the third

26   and the fourth quartile of LAP were more likely to develop prehypertension and

27   hypertension than those with the first quartile in both males and females.

28   After adjusting for age, marital status, and educational level, the risks of

10

1   prehypertension (adjusted OR: 3.14, 95% CI: 1.95–5.07) and hypertension (adjusted

2   OR: 9.02; 95% CI: 5.11–15.93) significantly increased in male participants with the

3   fourth quartile compared with those with the first quartile. For females, increasing

4   risks of prehypertension (adjusted OR: 3.26, 95% CI: 2.09–5.10) and hypertension

5   (adjusted OR: 6.32; 95% CI: 3.42–11.65) were observed in participants with the

6   fourth LAP quartile compared with those with the first one.

7   After controlling for age, marital status, educational level, physical activity,

8   smoking, alcohol consumption, BMI, WHR, fasting plasma glucose, and family

9   history of hypertension, the risks of prehypertension (adjusted OR: 1.67, 95% CI:

10   0.96–2.92) and hypertension (adjusted OR: 2.79, 95%CI: 1.43–5.44) significantly

11   increased in male participants with the fourth quartile compared with those with the

12   first quartile. Meanwhile, increasing risks of prehypertension (adjusted OR: 2.10, 95%

13   CI: 1.26–3.51) and hypertension (adjusted OR: 3.15, 95%CI: 1.56–6.39) were

14   observed in female participants with the fourth LAP quartile compared with those

15   with the first one.

16   The results of ROC curves analysis in males and females were shown in Figure. 1

17   and 2 and Table 5. LAP (AUC = 0.721; 95% CI: 0.680–0.761) was a better indicator

18   to predict different types of hypertension than BMI (AUC = 0.698; 95% CI:

19   0.658–0.737) ,WHR (AUC = 0.684; 95% CI: 0.643–0.726) and TG (AUC = 0.663;

20   95% CI: 0.620–0.706) in females; however, WC (AUC = 0.734 95% CI: 0.700–0.769)

21   performed better than BMI (AUC = 0.707, 95% CI: 0.672–0.742), WHR (AUC =

22   0.688; 95% CI: 0.650–0.725), LAP (AUC = 0.677; 95% CI: 0.640–0.713) and TG

23   (AUC = 0.607; 95% CI: 0.568–0.646) on males. The best cut-off values of LAP to

24   predict hypertension were 63.892 in males and 30.860 in females.

25   **Interaction effects between LAP and family history of hypertension**

26   The interaction effects between LAP and family history of hypertension are presented

27   in Table 6. Significant interaction effects between LAP and family history of

28   hypertension were observed in males. The results of RERI (1.652; 95% CI:

29   0.267–3.037) and AP (0.516; 95% CI: 0.238–0.794) indicated a significant interaction

1 effect of family history of hypertension and LAP on hypertension, but the result of SI

2 (3.998; 95% CI: 0.897–17.820) did not.

3 However, no statistically significant interaction effects were found between LAP

4 and family history of hypertension in females, which is indicated by all the three

5 indicators. RERI was - 0.673 (95% CI: -2.566–1.220); AP was -0.328 (95% CI:

6 -1.451–0.795); and SI was 0.610 (95% CI: 0.125–2.979).

7 **Discussion**

8 With the rapid development of the economy and sedentary lifestyle, elevated blood

9 pressure has become a common and serious public health issue.[31] The prevalence of

10 prehypertension and hypertension significantly increased.[32] Elevated blood pressure is

11 caused by diverse factors, among which obesity is closely related to hypertension.[33]

12 The prevalence of obesity increased by 13% in urban areas and by 85% in rural areas

13 in China, and more attention should thus be paid to this issue.[17] Extensive studies

14 found that obesity, especially visceral adipose tissue, could strongly increase the

15 blood pressure.[33]

16 The mechanisms underlying the interaction between obesity and hypertension are

17 complicated. The mechanisms of obesity-induced hypertension include sodium

18 retention, insulin resistance, activation of renin-angiotensin-aldosterone, altered

19 vascular function, and secretion of relevant adipokines.[34] Besides, the mechanisms of

20 blood pressure increase can be activated by visceral fat.[35]

21 Substantial evidence proved that the harm of the fat accumulation was greater than

22 the total amount of fat.[36, 37] However, traditional obesity indexes, such as BMI, WC,

23 and WHR, have limitations of distinguishing differences between subcutaneous fat

24 and visceral fat. Therefore, a new obesity index that can predict visceral fat easily and

25 effectively is urgently needed. After Kahn first demonstrated that LAP performs

26 better than BMI for recognizing the cardiovascular risk, domestic and foreign scholars

27 paid increasing attention to LAP. LAP, a combination of WC and TG, is an accessible

28 and inexpensive way to assess visceral fat.[13] It is a well-known fact that TG reflect the

12

degree of visceral fat accumulation and WC strongly associated with hypertension.[12] Notably, hypertriglyceridemic waist (HTGW) is also calculated based on the combination of TG and WC. However, LAP, as a continuous indicator, is superior to reflect visceral fat than HTGW,[38] a discontinuous indicator.[21] Therefore, LAP was used as a visceral obesity indicator in this study.

LAP is based on the hypothesis of minimum waist circumference includes the rachis, abdominal viscera and muscle.[13] Therefore, the differences between the actual WC and the minimum WC can represent abdominal adipose tissue.[13] Notably, LAP in almost all studies is calculated by data obtained based on the third National Health and Nutrition Examination Survey in the United States.[13] Because of differences in race, dietary habits, or lifestyle, individuals from different countries should have different visceral adipose tissues. It demonstrated that there are considerable differences in visceral adipose tissues between Chinese individuals and Europeans or Americans.[39] Therefore, LAP was calculated in our study using a modified formula so that it could apply to the individuals dwelling in Southern China.

As expected, a significant association was found between LAP and hypertension in the present study. Our findings are consistent with those in studies by Zhong et al,[17] Song et al,[37] and Shen et al,[22] all of which have demonstrated that LAP is an effective and reliable diagnostic indicator of hypertension. Participants with significantly higher LAP had higher risks of prehypertension and hypertension than those with lower LAP. Multinomial logistic regression analysis revealed that after adjusting for other factors, the risks of prehypertension and hypertension in the group with the highest LAP level were 2.10 and 3.15 times higher in females, respectively, than those in the group with the lowest LAP.

Wang et al.found LAP is a better index to predict the risk of hypertension.[40] However, Gao et al found that the performance of LAP was superior to that of BMI in male Mongolians;[23] this findings may be due to the apparently lower prevalence of high TG in female Mongolians than in male Mongolians (13.20% vs 23.10%，$P < 0.05$), and the facts might disturb the association between LAP and hypertension in

female Mongolians. Several studies found the superiority of LAP over BMI for detection of hypertension and prehypertension in both genders.[21, 37, 40] However, in the present study, we also found that LAP perform better than BMI in female. According to Kahn,[41] the annual LAP changes were reduced at older age in male. Advancing age is associated with a progressive increase in systolic BP levels and with development and progression of arterial hypertension because of a number of factors, including atherosclerotic changes, large artery stiffening, altered renal function, and arterial baroreflex impairmen,[42] That is to say, increase in blood pressure was thought to be an unavoidable consequence of aging. Thus, the superiority of LAP for predicting hypertension in male may be disturbed by the larger-scale proportion of elder man (23.7%) in our study. In our study, LAP perform better in predicting the hypertension risk than TG in both sex. However, due to low predictive value of TG in southern China, LAP which combines of TG and WC is slightly inferior to WC.

In general, LAP, which applied to the Southern Chinese population, was a better indicator for predicting the hypertension risk in females in this study. In addition, large studies have demonstrated that family history of hypertension is a critical risk factor for hypertension, and individuals with family history of hypertension are 2–4 times more likely to develop hypertension than those without the family history of hypertension.[43] The interaction analysis in this study indicates the synergistic effect of LAP and family history on the hypertension risk in males, but no statistically significant differences in the interaction effect in females. This findings might be due to the fact there was no statistically significant difference between females and the family history of hypertension in our study (χ^2=6.847，P=0.0355>0.05). In fact, cardiovascular events occur at a lower rate in females than in males.[44] In our study, the female participants who had both LAP and family history of hypertension were rarely observed and the prevalence rates of hypertension at a lower rate in females than in males no matter premenopausal status or menopausal status.[45] Our study suffers from a small sample size, especially in females. The fewer positive female observers which had higher LAP and family history of hypertension lead to no

14

1   statistically significant differences in the interaction effect on the hypertension risk in

2   females. The interaction in female was not statistically significant, but their

3   synergistic effect was obvious. The synergistic effect between family history of

4   hypertension and LAP on the hypertension risk was demonstrated in our study as well

5   as in other studies.[21, 40] Visceral obesity and family history of hypertension may result

6   in increased blood pressure through some unknown mechanisms. However, further

7   studies are needed to investigate the interaction effect between LAP and family

8   history of hypertension on the hypertension risk.

9   To date, LAP is an inexpensive screening tool to identify visceral adipose tissue,

10 and the method has high reproducibility. LAP, which was proposed by Kahn, was

11 developed for the Western population. Thus this study explored the validity of LAP,

12 which was calculated based on the Southern China population, and the interactive

13 effects of LAP and family history of hypertension. The findings suggest LAP might

14 perform better in predicting the hypertension risk than BMI, WHR and TG in

15 Southern Chinese females. Furthermore, the interaction analysis in this study indicates

16 the synergistic effect of LAP and family history on the hypertension risk. Although,

17 the interaction in female was not statistically significant, their synergistic effect was

18 obvious.

19 This study has some limitations. First of all, because this is a cross-sectional study,

20 the present results are not sufficient to indicate causality. Secondly, the population of

21 our study can partially represent the general population in the Southern China, but can

22 not fully represent this region. Furthermore, this article is lack of adjustment for renal

23 function, and other risk factors for hypertension (such as serum uric acid). Finally,

24 because of the small sample size in this study, further studies with a larger sample size

25 are needed to investigate whether the modified LAP applies to all the residents

26 dwelling in Southern China.

27 **CONCLUSION**

28 In conclusion, LAP significantly associated with the hypertension risk, and higher

29 LAP levels had relatively higher blood pressure. LAP performed better in predicting

15

hypertension of the Southern China female population than BMI, WHR, and TG did. Moreover, LAP and family history of hypertension might synergistically increase the risk of hypertension.

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Contributors

Jun-Xuan Huang, Pei-Xi Wang and Jin-Xiang Ma conceived and designed the study. Jun-Xuan Huang, Xin-Yu Bao, Yi-Xian Xie, Xiao-Xia Zhang, Xin Peng, Yan Liu and Meng-Jiao Cheng contributed to collection of the data, analyzed the data and interpretation of the results. Jun-Xuan Huang wrote the draft manuscript. Jin-Xiang Ma, Pei-Xi Wang and Jun-Xuan Huang finalized the manuscript with inputs from all authors. All of the authors approved the final version submitted for publication.

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Competing interests

The authors declared that they had no conflict of interest.

Ethics statement

This study was approved by the Ethics Committee of Guangzhou Medical University. Written informed consent was obtained from each study participant before investigation.

Data sharing statement

Our data might not be shared directly, because it's our team work and the data belongs

to our team. Thus consent should be attained from team members.

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25 **The titles and legends of figure**

26 **Title**

27 **Fig.1** The ROC curve of different obesity indexes in predicting hypertension in males.

28 **legend**

29 LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC:

30 waist circumference; TG: Triglyceride.

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2 **Title**

3 **Fig.2** The ROC curve of different obesity indexes in predicting hypertension in

4 females.

5 **legend**

6 LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC:

7 waist circumference; TG: Triglyceride.

22

1   **Table 1** Basic characteristics of the participants

Variables	Normotension (N = 832)	Prehypertension (N = 789)	Hypertension (N = 458)	χ^2 / Z	*P*-value
Sex (%)				135.625	< 0.001
Male	32.57	58.68	58.52		
Female	67.43	41.32	41.48		
Age (years)	36.42 ± 10.59	41.38 ± 12.71	48.93 ± 12.75	267.206	< 0.001
Marital status (%)				21.287	< 0.001
Currently not married	23.20	18.76	12.66		
Currently married	76.80	81.24	87.34		
Education level (%)				101.355	< 0.001
Elementary school and lower	15.87	21.55	36.46		
Secondary school	36.30	38.53	39.96		
Senior high school and higher	47.83	39.92	23.58		
Physical activity (%)				2.688	0.611

Seldom or never	35.70	34.22	31.22		
Moderate	17.43	18.25	18.78		
High	46.87	47.53	50.00		
Smoker (%)				50.346	< 0.001
Non-smoker	82.25	71.61	67.90		
Smoker	16.18	26.87	28.61		
Former smoker	0.97	1.52	3.49		
Drinker (%)				30.865	< 0.001
Non-drinker	84.11	76.34	72.53		
Drinker	14.91	22.39	24.62		
Former drinker	0.98	1.27	2.85		
BMI				255.012	< 0.001
< 18.5	13.70	5.20	2.18		
18.5–23.9	68.51	54.88	41.70		
24–27.9	14.30	31.69	37.55		

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≥ 28	3.49	8.24	18.56		
WC	75.61±8.19	81.61±9.04	87.02±9.95	411.441	< 0.001
WHR	0.85± 0.06	0.88± 0.07	0.91± 0.06	248.475	< 0.001
Fasting plasma glucose (mmol/L)	4.69 ± 0.82	4.98 ± 1.33	5.31 ± 1.86	90.399	< 0.001
Total cholesterol (mmol/L)	4.70 ± 0.96	4.98 ± 1.07	5.26 ± 1.15	88.325	< 0.001
Triglyceride (mmol/L)	1.26 ± 0.83	1.77 ± 1.77	2.15 ± 2.25	178.995	< 0.001
Systolic blood pressure (mmHg)	107.97 ± 7.80	125.45 ± 6.65	144.78 ± 18.55	1533.137	< 0.001
Diastolic blood pressure (mmHg)	69.49 ± 6.40	79.59 ± 5.99	91.49 ± 11.33	1206.505	< 0.001
Family history of hypertension (%)				18.391	0.005
Only father	11.42	11.03	11.14		
Only mother	12.02	15.08	17.25		
Both parents	5.41	4.82	8.95		
Neither	71.15	69.07	62.66		
LAP	29.14 ± 27.00	52.15 ± 63.50	75.87 ± 99.81	355.133	< 0.001

1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

1   **Table 2** Basic characteristics of the participants

Variables	Male					Female				
	Normotension **(N = 271)**	**Prehypertension** **(N = 463)**	**Hypertension** **(N = 268)**	**χ^2 / Z**	**_P_-value**	**Normotension** **(N = 561)**	**Prehypertension** **(N = 326)**	**Hypertension** **(N = 190)**	**χ^2 / Z**	**_P_-value**
Age (years)	36.57 ± 11.02	39.90 ± 12.37	47.15 ± 12.95	91.532	< 0.001	36.35 ± 10.39	43.48 ± 12.92	51.43 ± 12.11	201.378	< 0.001
Marital status (%)				26.019	< 0.001				7.928	0.019
Currently not married	31.37	22.46	13.06			19.25	13.50	12.11		
Currently married	68.63	77.54	86.94			80.75	86.50	87.89		
Education level (%)				24.179	< 0.001				116.258	< 0.001
Elementary school and lower	15.13	15.33	25.00			16.22	30.37	52.63		
Secondary school	37.64	40.39	45.15			35.65	35.89	32.63		
Senior high school and higher	47.23	44.28	29.85			48.13	33.74	14.74		
Physical activity (%)				0.807	0.668				2.979	0.226
insufficiently active	58.30	56.16	54.48			50.62	47.24	43.68		

sufficiently active	41.70	43.84	45.52			49.38	52.76	56.32		
Smoker (%)				7.037	0.132				5.893	0.122
Non-smoker	47.78	52.27	46.27			99.82	99.08	99.42		
Smoker	49.26	45.36	48.13			0.18	0.61	1.05		
Former smoker	2.96	2.38	5.60			0.00	0.31	0.53		
Drinker (%)				3.790	0.432				4.993	0.255
Non-drinker	60.74	61.47	57.30			95.62	97.53	94.15		
Drinker	36.67	36.36	38.20			4.20	2.47	5.32		
Former drinker	2.59	2.16	4.49			0.18	0.00	0.53		
BMI				148.700	< 0.001				99.205	< 0.001
< 18.5	16.61	4.54	1.49			12.30	6.13	3.16		
18.5–23.9	65.68	54.64	38.43			69.88	55.21	46.32		
24–27.9	14.39	33.26	39.18			14.26	29.45	35.26		
≥ 28	3.32	7.56	20.90			3.57	9.20	15.26		
WC	77.26±7.85	82.95±8.49	88.71±9.43	193.623	< 0.001	74.82±8.24	79.72±9.46	84.63±10.20	154.819	< 0.001

WHR	0.86±0.06	0.89±0.06	0.92±0.06	126.195	< 0.001	0.84±0.07	0.86±0.07	0.89±0.06	183.524	< 0.001
Fasting plasma glucose (mmol/L)	4.76 ± 1.08	4.98 ± 1.38	5.30 ± 1.94	24.275	< 0.001	4.65 ± 0.66	4.99 ± 1.26	5.31 ± 1.75	71.169	< 0.001
Total cholesterol (mmol/L)	4.73 ± 1.00	4.98 ± 1.06	5.17 ± 1.25	20.500	< 0.001	4.69 ± 0.94	4.98 ± 1.08	5.39 ± 0.98	73.075	< 0.001
Triglyceride (mmol/L)	1.54 ± 1.08	1.93 ± 1.94	2.38 ± 2.68	40.974	< 0.001	1.12 ± 0.64	1.54 ± 1.47	1.82 ± 1.40	90.583	< 0.001
Systolic blood pressure (mmHg)	110.52 ± 6.13	125.60 ± 6.54	145.64 ± 17.04	706.430	< 0.001	106.73 ± 8.21	125.23 ± 6.81	143.57± 20.48	755.356	< 0.001
Diastolic blood pressure (mmHg)	70.82 ± 5.79	80.27 ± 5.75	93.11 ± 10.66	592.747	< 0.001	68.84 ± 6.59	78.63 ± 6.19	89.20 ± 11.87	553.348	< 0.001
Family history of hypertension (%)				16.427	0.012				6.847	0.335
Only father	10.70	11.23	13.81			11.76	10.74	7.37		
Only mother	11.44	17.28	18.28			12.30	11.96	15.79		
Both parents	6.27	4.75	9.70			4.99	4.91	7.89		
Neither	71.59	66.74	58.21			70.94	72.39	68.95		
LAP	38.69 ± 34.85	58.43 ± 65.52	87.83 ± 120.94	113.508	< 0.001	24.52 ± 20.75	43.24 ± 59.48	58.98 ± 54.19	159.320	< 0.001

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1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

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6   **Table 3** Comparison of blood pressure among four quartiles of LAP

Variables	LAP				Z	*P*-value
	Q1	Q2	Q3	Q4		
Male						
Systolic blood pressure (mmHg)	119.33 ± 13.72	125.61 ± 14.86	129.23 ± 16.38	133.36 ± 17.85	106.793	< 0.001
Diastolic blood pressure (mmHg)	75.84 ± 9.89	80.55 ± 9.84	82.56 ± 10.74	85.64 ± 11.36	106.285	< 0.001
Female						
Systolic blood pressure (mmHg)	110.45 ± 13.91	114.95 ± 15.07	119.66 ± 15.91	130.25 ± 19.78	184.926	< 0.001
Diastolic blood pressure (mmHg)	71.05 ± 9.45	73.29 ± 9.60	76.21 ± 9.96	81.04 ± 11.70	134.730	< 0.001

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2 **Table 4** Multinomial logistic regression analysis of LAP associated with hypertension status

Quartiles of LAP	OR[a](95% CI)		OR[b](95% CI)		OR[c](95% CI)	
	prehypertension	hypertension	prehypertension	hypertension	prehypertension	hypertension
Male						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	2.98***	4.70***	2.22***	2.38**	1.73*	1.61
	(1.88, 4.72)	(2.34, 9.45)	(1.48, 3.34)	(1.36, 4.16)	(1.12, 2.67)	(0.89, 2.94)
Q3	4.48***	8.26***	2.68***	3.90***	1.66*	1.75
	(2.85, 7.03)	(4.21, 16.21)	(1.74, 4.12)	(2.24, 6.82)	(1.03, 2.68)	(0.94, 3.26)
Q4	4.65***	17.82***	3.14***	9.02***	1.67	2.79***
	(2.93, 7.36)	(9.21, 34.46)	(1.95, 5.07)	(5.11, 15.93)	(0.96, 2.92)	(1.43, 5.44)
Female						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	1.75**	2.19**	1.046	1.19	0.91	1.015
	(1.22, 2.51)	(1.27, 3.77)	(0.69,1.58)	(0.62,2.29)	(0.59,1.41)	(0.51,2.03)

Q3	3.35***	6.50***	1.68**	1.87	1.31	1.19
	(2.27, 4.93)	(3.83, 11.02)	(1.11,2.52)	(0.99,3.49)	(0.84,2.05)	(0.60,2.38)
Q4	5.99***	20.06***	3.26***	6.32***	2.10**	3.15***
	(3.74, 9.59)	(11.37, 35.38)	(2.09,5.10)	(3.42,11.65)	(1.26,3.51)	(1.56,6.39)

1   OR=Odds ratio; CI=confidence interval; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

2   [a], unadjusted.

3   [b], adjusted for age, sex, marital status, educational level

4   [c], adjusted for physical activity, smoker, drinker, BMI, WHR, fasting plasma glucose, family history of hypertension, and all the factors in b.

5

6   **Table 5** Predicting hypertension by different obesity indexes

Variables	Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index	AUC(95% CI)	*P*-value
Male						
BMI	23.004	73.51	58.08	0.316	0.707 (0.672, 0.742)	< 0.001
WHR	0.906	58.58	70.27	0.289	0.688 (0.650, 0.725)	< 0.001
LAP	63.892	49.63	76.99	0.266	0.677 (0.640, 0.713)	< 0.001

WC	85.05	65.67	72.60	0.383	0.734 (0.700, 0.769)	< 0.001
TG	1.91	46.27	70.14	0.164	0.607 (0.568, 0.646)	< 0.001
Female						
BMI	21.767	81.58	50.73	0.323	0.698 (0.658, 0.737)	< 0.001
WHR	0.860	74.21	55.24	0.294	0.684 (0.643, 0.726)	< 0.001
LAP	30.860	68.95	67.42	0.363	0.721 (0.680, 0.761)	< 0.001
WC	79.90	72.11	64.94	0.370	0.725 (0.686, 0.766)	< 0.001
TG	1.26	63.68	64.49	0.282	0.663 (0.620, 0.706)	< 0.001

1 BMI: body mass index; WHR: waist-hip rate; LAP: lipid accumulation product; WC: waist circumference; TG: Triglyceride; AUC: area under curve;

2 OR=Odds ratio; CI=confidence interval.

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4 **Table 6** Interaction effects between LAP and family history of hypertension

Variables	**Variables**	**N**	**OR[c] (95% CI)**	**Interaction indexes (95% CI)**
Male				
LAP[a]	Family history[b]			

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LAP[a]	Family history[b]			
-	-	486	1 (reference)	RERI = 1.652 (0.267, 3.037)[*]
-	+	215	1.189 (0.772, 1.832)	AP = 0.516 (0.238, 0.794)[*]
+	-	173	1.362 (0.875, 2.121)	SI = 3.998 (0.897, 17.820)
+	+	128	3.203[***] (2.002, 5.124)	

Female

LAP[a]	Family history[b]			
-	-	657	1 (reference)	RERI = -0.673 (-2.566, 1.220)
-	+	276	1.995[**] (1.284, 3.099)	AP = -0.328 (-1.451, 0.795)
+	-	108	1.729[*](1.023, 2.922)	SI = 0.610 (0.125, 2.979)
+	+	36	2.051 (0.919, 4.589)	

1   LAP: lipid accumulation production; RERI: relative excess risk of interaction ; AP: attributable proportion due to interaction; SI: synergy index; OR=Odds
2   ratio; CI=confidence interval; [***], $P < 0.001$; [**], $P < 0.01$; [*], $P < 0.05$.

3   [a], grouped by the cut-off values in Table 4.

4   [b], family history of hypertension was defined as one parent or both parents having hypertension.

5   [c], adjusted for age, marital status, educational level, physical activity, smoker, drinker, BMI, and WHR.

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Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.
legend
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

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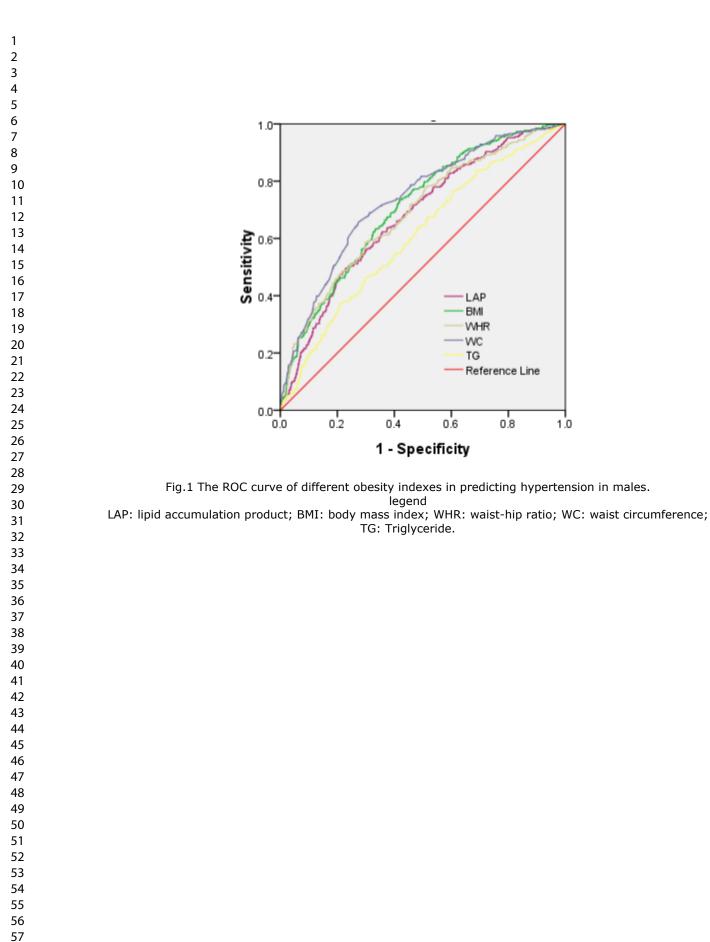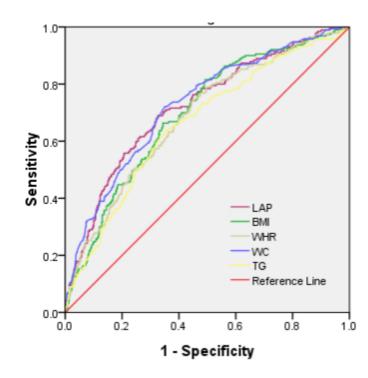60

Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.legendLAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 3

Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7-8
		(*c*) Explain how missing data were addressed	Page 5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8-9; Table 1; Table 2
		(b) Give reasons for non-participation at each stage	Not application
		(c) Consider use of a flow diagram	Not application
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9; Table 1; Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Not application
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8-9; Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-10; Table 4; Table 6
		(*b*) Report category boundaries when continuous variables were categorized	Page 6-8; Table 1; Table 2; Table 3 ;

			Table 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not application
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11; Table 6
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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1

Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population

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2

1 **ABSTRACT**

2 **Objectives:** This study aimed at investigating the applicability of a novel index based

3 on waist circumference (WC) and Triglyceride (TG) which was named lipid

4 accumulation product (LAP) in the Southern Chinese population, and compared the

5 predictive effects of LAP and other obesity indicators on hypertension risk. Moreover,

6 this study investigated the interactive effects of LAP and family history of

7 hypertension.

8 **Methods:** A total number of 2079 of community-dwelling adults in Southern China

9 were enrolled in this cross-sectional study. The participants underwent questionnaire

10 surveys, anthropometric tests, and laboratory examinations. The multivariate logistic

11 regression model and receiver operating characteristic (ROC) curves, including LAP,

12 body mass index (BMI), waist-hip ratio (WHR), WC, and TG were used to assess the

13 association between hypertension risk and obesity indexes. The interaction effects

14 were evaluated by relative excess risk of interaction (RERI), attributable proportion

15 due to interaction (AP), and synergy index (SI).

16 **Results:** Higher LAP levels have a relatively higher risk of having hypertension in

17 both sexes (males: adjusted odds ratio [OR] = 2.79 per SD increase, 95% confidence

18 interval [CI] = 1.43-5.44, $P < 0.001$; females: adjusted OR:3.15,95%CI=1.56-6.39, P

19 < 0.001). LAP (area under curve [AUC] = 0.721; 95% CI: 0.680–0.761) is a better

20 indicator in identifying hypertension risk than BMI, WHR, and TG in females, but

21 WC performed better in males. A significant interaction between LAP and family

22 history of hypertension was observed in males (RERI = 1.652, 95% CI: 0.267–3.037;

23 AP = 0.516, 95% CI: 0.238–0.794; SI = 3.998, 95% CI: 0.897–17.820), but there is no

24 statistically significant differences in females.

25 **Conclusions:** LAP significantly associates with hypertension risk in the Southern

26 Chinese population. It has better performance than BMI, WHR, and TG on predicting

27 hypertension risk of the Southern Chinese female population. Moreover, LAP and

28 family history of hypertension might synergistically increase the risk of hypertension.

3

1 **Keywords: Hypertension, LAP, Family history, Interaction effect**

2 **Strengths and limitations of this study**

3 **Strengths**:

4 1. Our study is the first to examine the validity of LAP, which is calculated using a

5 modified formula, in the Southern China population.

6 **Limitations:**

7 1. This is a cross-sectional study; the results are not sufficient to indicate causality.

8 2. The population of our study can partially represent the general population in the

9 Southern China but cannot fully represent this region.

10 3. This study lacks of the adjustment for renal function, and other risk factors for

11 hypertension (such as serum uric acid) .

12 4. This study has small sample size, so further studies with a larger sample size are

13 needed to investigate whether the modified LAP applies to all the residents dwelling

14 in Southern China.

4

INTRODUCTION

Hypertension, a significant risk factor of cardiovascular disease,[1] is one of the most prevalent public health problems in the world and is the leading contributor to the global burden of disease and mortality. Nowadays, the number of adults with hypertension in the world is being predicted to increase by about 60% to a total of 1.56 billion in 2025, and one-third of adults are suffering from hypertension in China.[2, 3]

Obesity, especially visceral fat, and family history of hypertension contributes to hypertension significantly.[4-6] Numerous studies agree on the idea that people with hypertension's family history have higher chance to get hypertension.[6-9] Usually, when it comes to obesity, the indexes that are most frequently used to assess obesity are body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR); however, these traditional obesity indexes merely reflect the degrees of overweight and abdominal obesity, also, cannot distinguish the difference between subcutaneous fat and visceral fat.[10] Micromagnetic resonance imaging and microcomputed tomography, which are the visceral fat golden standard measurement methods, is inconvenient and expensive.[11] Moreover, they are not suitable for large-scale epidemiological investigations. Therefore, it is necessary to discover a new obesity indicator that can predict visceral fat from subcutaneous fat more conveniently and economically.

Recently, increasing attention has been directed towards lipid accumulation product (LAP). LAP, a new obesity index computed from WC and triglyceride (TG), is a useful indicator of visceral fat,[12] as demonstrated by Kahn in 2005[13]. Some studies suggest that LAP can also be used to identify metabolic syndromes,[14, 15] type 2 diabetes mellitus,[16] stroke,[17] and arterial stiffness.[18] Additionally, several cross-sectional studies conducted in Japan,[19] India,[14] and Brazil indicate that LAP significantly associated with cardiovascular disease and is a better indicator than BMI for identifying cardiovascular risk.[13, 20] A few national studies have investigated the association between LAP and hypertension in China, and all of them are conducted in

1   northern China, including Bengbu,[21] Beijing,[22] and Inner Mongolia.[23] With a vast

2   territory, China has a tremendous difference between South and North. Due to the

3   geographical environment and dietary habits that have formed throughout its long

4   history, there are some dietary and cultural differences between Northern and

5   Southern China.[24] The Northern region shows a high intake of wheat, tubers, and

6   liquor, etc. While southerner has a high intake of rice, vegetables, meat, poultry, fish

7   etc.[24] The Carbohydrate-rich pattern of the northern region is associated with a high

8   risk of hypertriglyceridemia and higher BMI. Meanwhile, significant differences are

9   found in systolic blood pressure (SBP)/diastolic blood pressure (DBP) between

10   southern Chinese and northern Chinese owing to different climate and dietary habits

11   between southern and northern.[25] Studies have found that the northerners are heavier

12   and have higher triglycerides level than southerners.[26, 27] Differences in dietary habits,

13   or lifestyle, individuals from different regions should lead to different LAP. LAP has

14   a different situation in the north and south. Thus, the applicability of LAP in

15   predicting hypertension in Southern China is worth studying. However, rare studies

16   have compared LAP with other obesity indexes in the Southern Chinese population.

17   Besides, almost all studies about LAP are using the formula based on the third

18   National Health and Nutrition Examination Survey in the US. Therefore, it is

19   reasonable to suggest that the calculation formula of LAP needs to be modified in the

20   Chinese population.

21   To the best of our knowledge, no studies have attempted to adjust the calculation

22   formula of LAP so that it can apply to the Southern Chinese population, and rare

23   studies have explored additive interactions between family history of hypertension

24   and LAP. Thus, the primary purpose of this study was to investigate the applicability

25   of LAP in the Southern Chinese population and compare the predictive effects of LAP

26   and other obesity indicators on hypertension risk. The secondary purpose of the study

27   was to assess interactive effects between LAP and family history of hypertension to

28   predict the hypertension risk in the Southern Chinese population.

29   **METHODS**

6

Study design and subjects

A cross-sectional survey based on community health was conducted in the Foshan city of Guangdong province in Southern China. Recruiting the enrollers took place on March 2017. The study samples were selected by a multistage and stratified random sampling method. The stratification according to the economic levels and randomly selected urban and rural at economic levels, then randomly selected communities according to proportion of urban and rural. Communities residents were then randomly selected from the household lists. A total of 3760 individuals were enrolled in this study; among them, 1681 participants who lacked complete data on demographic characteristics, anthropometric tests, or laboratory examinations were excluded. There were no statistically significant differences in age and sex between excluded participants and included participants. Finally, 2079 adults who had complete data were included in the analysis.

Patient and public involvement

Patients or public were not involved in this study.

Ethics statement

This study was approved by the Ethics Committee of Guangzhou Medical University. Written informed consent was obtained from each study participant before investigation.

General study questionnaire

An interview-based survey was performed using a questionnaire by trained staff. Socio-demographic data, family history of hypertension, cigarette smoking, and alcohol drinking were investigated. Smokers were defined as the participants smoking at least 1 cigarette/day for at least 6 months. Drinkers were defined as individuals consuming at least 30 ml alcohol/week for 1 year or more. Physical activities were divided into "insufficiently active" and "sufficiently active." Participants with "insufficiently active" were defined as those who performed activity less than 150 min/week. Participants with "sufficiently active" were defined as those who exercised

more than 150min/week.[28] Marital status was classified as "currently not married" and "currently married"; "married" was regarded as "currently married," and "divorced/widowed/single" was regarded as "currently not married." Educational level was categorized as "elementary school or lower," "secondary school," and "senior high school or higher."

Anthropometric tests and laboratory examinations

The participants were required to take off their shoes and wear lightweight clothing for weight and height measurements. WC was measured at the level of 1 cm above the navel.[29] Automatic sphygmomanometer (OMRON, hem-7125) was used to measure blood pressure (BP) of participants. BP measurement was conducted thrice in a quiet environment, and the participants rested at least one minute between each time of measurement. The mean of the three measurements was used in the analysis. Prehypertension was defined as SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, and hypertension was defined as SBP of $\geq$ 140 mmHg, DBP of $\geq$ 90 mmHg, and/or a reported medical history of anti-hypertensive medication.[29] The BMI was calculated as weight in kilograms divided by the square of the height in meters. Overweight was defined as BMI of 24–27.9 kg/m^2, and obesity was defined as BMI of $\geq$ 28 kg/m^2. The fasting blood samples were collected from the participants in the morning after an overnight fast and were used to assess fasting plasma glucose, total cholesterol, and TG levels.

According to Kahn's theory,[13] LAP is calculated as [WC (cm) - The minimum of WC (male)] $\times$ [TG (mmol/L)] for males and [WC (cm) - The minimum of WC (female)] $\times$ [TG (mmol/L)] for females, and the minimum waist size theoretically contains only the abdomen, muscle, viscera, and vertebral bone.[13] Visceral fat can be estimated by the difference between the WC and the minimum waist size. In the present study, the WC of the studied population was skewed; therefore, the WC was log-transformed. The minimum WC was estimated by the mean WC minus two standard deviations after log-transformation in the local participants aged 18–24 years.[13, 22]

1 **Statistical analyses**

2 According to the hypertension status, the enrollees were divided into three groups

3 (normotension, prehypertension, and hypertension). The frequency (%) was used to

4 describe sex, marital status, education level, physical activity, BMI, smoker, and

5 drinker. Mean ± standard deviation (SDs) was used to describe the WC, WHR, fasting

6 plasma glucose, total cholesterol, TG, SBP, DBP, and LAP. LAP was divided into

7 four groups by the quartiles, i.e., Q1, Q2, Q3, and Q4. The differences of quantitative

8 data across different hypertension statuses were analyzed by the Kruskal-Wallis H test

9 because the data had skewed distribution. Categorical variables were analyzed by the

10 Chi-squared test. The multivariate logistic regression model was used to analyze the

11 relationship between LAP and risk factors of hypertension and prehypertension. The

12 receiver operating characteristics (ROC) curves were applied to identify the superior

13 obesity index and the best cut-off value of LAP to predict the hypertension risk.

14 Moreover, the interaction effects between LAP and family history of hypertension

15 were assessed by some relevant indicators, including the relative excess risk of

16 interaction (RERI = OR_{11} - OR_{10} - OR_{01} + 1), the attributable proportion due to

17 interaction (AP = [OR_{11} - OR_{10} - OR_{01} + 1]/OR_{11}), and the synergy index (SI = [OR_{11} -

18 1]/[OR_{01} - 1] + [OR_{10} - 1]). If the interaction effect was not observed, the confidence

19 interval of RERI and AP contained 0 and the confidence interval of S included 1.[30]

20 The above indicators were calculated using an Excel table designed by Andersson et

21 al.[30] All reported *P*-values were two-tailed, and a *P*-value of < 0.05 was considered

22 significant. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc.,

23 Chicago, IL, USA).

24 **RESULTS**

25 **LAP**

26 According to Kahn's theory,[13] LAP was calculated as (WC - 60.6) × (TG [mmol/L])

27 in males and (WC - 54.1) × (TG [mmol/L]) in females based on the actual data

28 obtained from the Southern Chinese population.[22]

Basic characteristics of the study participants

A total number of 2079 of adults with an average age of 41.06 years were enrolled in the present study, including 1002 males (48.29%) and 1077 females (51.80%). The overall prevalence rates of normotension, prehypertension, and hypertension were 40.02%, 37.95%, and 22.03%, respectively. Male participants had a high prevalence of prehypertension and hypertension than female participants ($P < 0.001$). Statistically significant differences in age ($P < 0.001$), marital status ($P < 0.001$), education level ($P < 0.001$), smoker ($P < 0.001$), drinker ($P < 0.001$), and family history of hypertension ($P = 0.005$) were observed between normotension, prehypertension, and hypertension groups. However, no significant differences were observed in physical activity ($P = 0.550$) among the three groups. Anthropometric measurements found significant differences in BMI ($P < 0.001$), WC ($P < 0.001$), WHR ($P < 0.001$), LAP ($P < 0.001$) between the groups. Statistically significant differences found in laboratory examinations including fasting plasma glucose ($P < 0.001$), total cholesterol ($P < 0.001$), SBP ($P < 0.001$), and DBP ($P < 0.001$) between the groups (Table 1). And the basic characteristics of different sex of study participants were shown in table 2.

LAP and the risk factors of hypertension

In order to investigate the relationship between LAP and blood pressure, LAP was divided into four groups by quartile in different sex (Table 3). A significant association was observed between LAP and blood pressure in both male and female. The results in males and females showed that SBP ($P < 0.001$) and DBP ($P < 0.001$) were relatively elevated in participants with higher LAP levels.

Multinomial logistic regression analysis was conducted to evaluate the association between LAP quartiles and hypertension status (Table 4). Participants with the third and the fourth quartile of LAP were more likely to develop prehypertension and hypertension than those with the first quartile in both males and females.

After adjusting for age, marital status, and educational level, the risks of

prehypertension (adjusted OR: 3.14, 95% CI: 1.95–5.07) and hypertension (adjusted

OR: 9.02; 95% CI: 5.11–15.93) significantly increased in male participants with the

fourth quartile compared with those with the first quartile. For females, increasing

risks of prehypertension (adjusted OR: 3.26, 95% CI: 2.09–5.10) and hypertension

(adjusted OR: 6.32; 95% CI: 3.42–11.65) were observed in participants with the

fourth LAP quartile compared with those with the first one.

After controlling for age, marital status, educational level, physical activity,

smoking, alcohol consumption, BMI, WHR, fasting plasma glucose, and family

history of hypertension, the risks of prehypertension (adjusted OR: 1.67, 95% CI:

0.96–2.92) and hypertension (adjusted OR: 2.79, 95%CI: 1.43–5.44) significantly

increased in male participants with the fourth quartile compared with those with the

first quartile. Meanwhile, increasing risks of prehypertension (adjusted OR: 2.10, 95%

CI: 1.26–3.51) and hypertension (adjusted OR: 3.15, 95%CI: 1.56–6.39) were

observed in female participants with the fourth LAP quartile compared with those

with the first one.

The results of ROC curves analysis in males and females were shown in Figure. 1

and 2 and Table 5. LAP (AUC = 0.721; 95% CI: 0.680–0.761) was a better indicator

to predict different types of hypertension than BMI (AUC = 0.698; 95% CI:

0.658–0.737) ,WHR (AUC = 0.684; 95% CI: 0.643–0.726) and TG (AUC = 0.663;

95% CI: 0.620–0.706) in females; however, WC (AUC = 0.734 95% CI: 0.700–0.769)

performed better than BMI (AUC = 0.707, 95% CI: 0.672–0.742), WHR (AUC =

0.688; 95% CI: 0.650–0.725), LAP (AUC = 0.677; 95% CI: 0.640–0.713) and TG

(AUC = 0.607; 95% CI: 0.568–0.646) on males. The best cut-off values of LAP to

predict hypertension were 63.892 in males and 30.860 in females.

Interaction effects between LAP and family history of hypertension

The interaction effects between LAP and family history of hypertension were

presented in Table 6. Significant interaction effects between LAP and family history

of hypertension were observed in males. The results of RERI (1.652; 95% CI:

0.267–3.037) and AP (0.516; 95% CI: 0.238–0.794) indicated a significant interaction

effect of family history of hypertension and LAP on hypertension, but the result of SI (3.998; 95% CI: 0.897–17.820) did not.

However, no statistically significant interaction effects were found between LAP and family history of hypertension in females, which was indicated by all the three indicators. RERI was - 0.673 (95% CI: -2.566–1.220); AP was -0.328 (95% CI: -1.451–0.795); and SI was 0.610 (95% CI: 0.125–2.979).

Discussion

With the rapid development of the economy and sedentary lifestyle, elevated blood pressure has become a common and serious public health issue.[31] The prevalence of prehypertension and hypertension significantly increased.[32] Elevated blood pressure is caused by diverse factors, among which obesity is closely related to hypertension.[33] The prevalence of obesity increased by 13% in urban areas and by 85% in rural areas in China, thus more attention should be paid to this issue.[17] Extensive studies found that obesity, especially visceral adipose tissue, could strongly increase the blood pressure.[33]

The mechanisms underlying the interaction between obesity and hypertension are complicated. The mechanisms of obesity-induced hypertension include sodium retention, insulin resistance, activation of renin-angiotensin-aldosterone, altered vascular function, and secretion of relevant adipokines.[34] Besides, the mechanisms of blood pressure increase can be activated by visceral fat.[35]

Substantial evidence has shown that the harm of the fat accumulation is greater than the total amount of fat.[36, 37] However, traditional obesity indexes, such as BMI, WC, and WHR, have limitations of distinguishing differences between subcutaneous fat and visceral fat. Therefore, a new obesity index that can predict visceral fat easily and effectively is urgently needed. After Kahn first has shown that LAP performs better than BMI for recognizing the cardiovascular risk, domestic and foreign scholars pay increasing attention to LAP. LAP, a combination of WC and TG, is an accessible and inexpensive way to assess visceral fat.[13] It is a well-known fact that TG reflects

12

the degree of visceral fat accumulation and WC strongly associates with hypertension.[12] Notably, hypertriglyceridemic waist (HTGW) is also calculated based on the combination of TG and WC. However, LAP, as a continuous indicator, is superior to reflect visceral fat than HTGW,[38] a discontinuous indicator.[21] Therefore, LAP is used as a visceral obesity indicator in this study.

LAP is based on the hypothesis of minimum waist circumference includes the rachis, abdominal viscera and muscle.[13] Therefore, the differences between the actual WC and the minimum WC can represent abdominal adipose tissue.[13] Notably, LAP in almost all studies is calculated by data obtained based on the third National Health and Nutrition Examination Survey in the United States.[13] Because of differences in race, dietary habits, or lifestyle, individuals from different countries should have different visceral adipose tissues. It is shown that there are considerable differences in visceral adipose tissues between Chinese individuals and Europeans or Americans.[39] Therefore, LAP is calculated in our study using a modified formula so that it could apply to the individuals dwelling in Southern China.

As expected, a significant association is found between LAP and hypertension in the present study. Our findings are consistent with those in studies by Zhong et al,[17] Song et al,[37] and Shen et al,[22] all of which have demonstrated that LAP is an effective and reliable diagnostic indicator of hypertension. Participants with significantly higher LAP have higher risks of prehypertension and hypertension than those with lower LAP. Multinomial logistic regression analysis reveals that after adjusting for other factors, the risks of prehypertension and hypertension in the group with the highest LAP level are 2.10 and 3.15 times higher in females, respectively, than those in the group with the lowest LAP.

Wang et al.found LAP is a better index to predict the risk of hypertension.[40] However, Gao et al found that the performance of LAP is superior to that of BMI in male Mongolians;[23] these findings may be due to the apparently lower prevalence of high TG in female Mongolians than in male Mongolians (13.20% vs 23.10%，$P < 0.05$), and the facts might disturb the association between LAP and hypertension in

female Mongolians. Several studies finds the superiority of LAP over BMI for detection of hypertension and prehypertension in both genders.[21, 37, 40] However, in the present study, we also found that LAP perform better than BMI in female. According to Kahn,[41] the annual LAP changes are reduced at older age in male. Advancing age is associated with a progressive increase in systolic BP levels and with development and progression of arterial hypertension because of a number of factors, including atherosclerotic changes, large artery stiffening, altered renal function, and arterial baroreflex impairmen,[42] That is to say, increase in blood pressure is thought to be an unavoidable consequence of aging. Thus, the superiority of LAP for predicting hypertension in male may be disturbed by the larger-scale proportion of elder man (23.7%) in our study. In our study, LAP performs better in predicting the hypertension risk than TG in both sex. However, due to low predictive value of TG in southern China, LAP which combines of TG and WC is slightly inferior to WC.

In general, LAP, which applied to the Southern Chinese population, is a better indicator for predicting the hypertension risk in females in this study. In addition, large studies have demonstrated that family history of hypertension is a critical risk factor for hypertension, and individuals with family history of hypertension are 2–4 times more likely to develop hypertension than those without the family history of hypertension.[43] The interaction analysis in this study indicates the synergistic effect of LAP and family history on the hypertension risk in males, but no statistically significant differences in the interaction effect in females. These findings might be due to the fact there was no statistically significant difference between females and the family history of hypertension in our study (χ^2=6.847，P=0.0355>0.05). In fact, cardiovascular events occur at a lower rate in females than in males.[44] In our study, the female participants who have both LAP and family history of hypertension are rarely observed and the prevalence rates of hypertension at a lower rate in females than in males no matter premenopausal status or menopausal status.[45] Our study suffers from a small sample size, especially in females. The fewer positive female observers which have higher LAP and family history of hypertension lead to no

14

1   statistically significant differences in the interaction effect on the hypertension risk in

2   females. The interaction in female is not statistically significant, but their synergistic

3   effect is obvious. The synergistic effect between family history of hypertension and

4   LAP on the hypertension risk is demonstrated in our study as well as in other

5   studies.[21, 40] Visceral obesity and family history of hypertension may result in

6   increased blood pressure through some unknown mechanisms. However, further

7   studies are needed to investigate the interaction effect between LAP and family

8   history of hypertension on the hypertension risk.

9   To date, LAP is an inexpensive screening tool to identify visceral adipose tissue,

10   and the method has high reproducibility. LAP, which is proposed by Kahn, is

11   developed for the Western population. Thus this study explored the validity of LAP,

12   which is calculated based on the Southern China population, and the interactive

13   effects of LAP and family history of hypertension. The findings suggest LAP might

14   perform better in predicting the hypertension risk than BMI, WHR and TG in

15   Southern Chinese females. Furthermore, the interaction analysis in this study indicates

16   the synergistic effect of LAP and family history on the hypertension risk. Although,

17   the interaction in female is not statistically significant, their synergistic effect is

18   obvious.

19   This study has some limitations. First of all, because this is a cross-sectional study,

20   the present results are not sufficient to indicate causality. Secondly, the population of

21   our study can partially represent the general population in the Southern China, but can

22   not fully represent this region. Furthermore, this article lacks of adjustment for renal

23   function, and other risk factors for hypertension (such as serum uric acid). Finally,

24   because of the small sample size in this study, further studies with a larger sample size

25   are needed to investigate whether the modified LAP applies to all the residents

26   dwelling in Southern China.

27   **CONCLUSION**

28   In conclusion, LAP significantly associates with the hypertension risk, and higher

29   LAP levels have relatively higher blood pressure. It has better performance than BMI,

1 WHR, and TG on predicting hypertension risk of the Southern Chinese female

2 population. Moreover, LAP and family history of hypertension might synergistically

3 increase the risk of hypertension.

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Contributors

9 Jun-Xuan Huang, Pei-Xi Wang and Jin-Xiang Ma conceived and designed the study.

10 Jun-Xuan Huang, Xin-Yu Bao, Yi-Xian Xie, Xiao-Xia Zhang, Xin Peng, Yan Liu and

11 Meng-Jiao Cheng contributed to collection of the data, analyzed the data and

12 interpretation of the results. Jun-Xuan Huang wrote the draft manuscript. Jin-Xiang

13 Ma, Pei-Xi Wang and Jun-Xuan Huang finalized the manuscript with inputs from all

14 authors. All of the authors approved the final version submitted for publication.

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Competing interests

19 The authors declared that they had no conflict of interest.

Ethics statement

21 This study was approved by the Ethics Committee of Guangzhou Medical University.

22 Written informed consent was obtained from each study participant before

23 investigation.

Data sharing statement

25 Our data might not be shared directly, because it's our team work and the data

26 belongs

27 to our team. Thus consent should be attained from team members.

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The titles and legends of figure

Title

Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.

legend

LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC:

waist circumference; TG: Triglyceride.

21

1

2 **Title**

3 **Fig.2** The ROC curve of different obesity indexes in predicting hypertension in

4 females.

5 **legend**

6 LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC:

7 waist circumference; TG: Triglyceride.

22

1 **Table 1** Basic characteristics of the participants

Variables	Normotension (N = 832)	Prehypertension (N = 789)	Hypertension (N = 458)	χ^2 / Z	*P*-value
Sex (%)				135.625	< 0.001
Male	32.57	58.68	58.52		
Female	67.43	41.32	41.48		
Age (years)	36.42 ± 10.59	41.38 ± 12.71	48.93 ± 12.75	267.206	< 0.001
Marital status (%)				21.287	< 0.001
Currently not married	23.20	18.76	12.66		
Currently married	76.80	81.24	87.34		
Education level (%)				101.355	< 0.001
Elementary school and lower	15.87	21.55	36.46		
Secondary school	36.30	38.53	39.96		
Senior high school and higher	47.83	39.92	23.58		
Physical activity (%)				2.688	0.611

Seldom or never	35.70	34.22	31.22		
Moderate	17.43	18.25	18.78		
High	46.87	47.53	50.00		
Smoker (%)				50.346	< 0.001
Non-smoker	82.25	71.61	67.90		
Smoker	16.18	26.87	28.61		
Former smoker	0.97	1.52	3.49		
Drinker (%)				30.865	< 0.001
Non-drinker	84.11	76.34	72.53		
Drinker	14.91	22.39	24.62		
Former drinker	0.98	1.27	2.85		
BMI				255.012	< 0.001
< 18.5	13.70	5.20	2.18		
18.5–23.9	68.51	54.88	41.70		
24–27.9	14.30	31.69	37.55		

24

≥ 28	3.49	8.24	18.56		
WC	75.61±8.19	81.61±9.04	87.02±9.95	411.441	< 0.001
WHR	0.85± 0.06	0.88± 0.07	0.91± 0.06	248.475	< 0.001
Fasting plasma glucose (mmol/L)	4.69 ± 0.82	4.98 ± 1.33	5.31 ± 1.86	90.399	< 0.001
Total cholesterol (mmol/L)	4.70 ± 0.96	4.98 ± 1.07	5.26 ± 1.15	88.325	< 0.001
Triglyceride (mmol/L)	1.26 ± 0.83	1.77 ± 1.77	2.15 ± 2.25	178.995	< 0.001
Systolic blood pressure (mmHg)	107.97 ± 7.80	125.45 ± 6.65	144.78 ± 18.55	1533.137	< 0.001
Diastolic blood pressure (mmHg)	69.49 ± 6.40	79.59 ± 5.99	91.49 ± 11.33	1206.505	< 0.001
Family history of hypertension (%)				18.391	0.005
Only father	11.42	11.03	11.14		
Only mother	12.02	15.08	17.25		
Both parents	5.41	4.82	8.95		
Neither	71.15	69.07	62.66		
LAP	29.14 ± 27.00	52.15 ± 63.50	75.87 ± 99.81	355.133	< 0.001

1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

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1   **Table 2** Basic characteristics of the participants

Variables	Male					Female				
	Normotension (N = 271)	Prehypertension (N = 463)	Hypertension (N = 268)	χ^2 / Z	*P*-value	Normotension (N = 561)	Prehypertension (N = 326)	Hypertension (N = 190)	χ^2 / Z	*P*-value
Age (years)	36.57 ± 11.02	39.90 ± 12.37	47.15 ± 12.95	91.532	< 0.001	36.35 ± 10.39	43.48 ± 12.92	51.43 ± 12.11	201.378	< 0.001
Marital status (%)				26.019	< 0.001				7.928	0.019
Currently not married	31.37	22.46	13.06			19.25	13.50	12.11		
Currently married	68.63	77.54	86.94			80.75	86.50	87.89		
Education level (%)				24.179	< 0.001				116.258	< 0.001
Elementary school and lower	15.13	15.33	25.00			16.22	30.37	52.63		
Secondary school	37.64	40.39	45.15			35.65	35.89	32.63		
Senior high school and higher	47.23	44.28	29.85			48.13	33.74	14.74		
Physical activity (%)				0.807	0.668				2.979	0.226
insufficiently active	58.30	56.16	54.48			50.62	47.24	43.68		

sufficiently active	41.70	43.84	45.52			49.38	52.76	56.32		
Smoker (%)				7.037	0.132				5.893	0.122
Non-smoker	47.78	52.27	46.27			99.82	99.08	99.42		
Smoker	49.26	45.36	48.13			0.18	0.61	1.05		
Former smoker	2.96	2.38	5.60			0.00	0.31	0.53		
Drinker (%)				3.790	0.432				4.993	0.255
Non-drinker	60.74	61.47	57.30			95.62	97.53	94.15		
Drinker	36.67	36.36	38.20			4.20	2.47	5.32		
Former drinker	2.59	2.16	4.49			0.18	0.00	0.53		
BMI				148.700	< 0.001				99.205	< 0.001
< 18.5	16.61	4.54	1.49			12.30	6.13	3.16		
18.5–23.9	65.68	54.64	38.43			69.88	55.21	46.32		
24–27.9	14.39	33.26	39.18			14.26	29.45	35.26		
≥ 28	3.32	7.56	20.90			3.57	9.20	15.26		
WC	77.26±7.85	82.95±8.49	88.71±9.43	193.623	< 0.001	74.82±8.24	79.72±9.46	84.63±10.20	154.819	< 0.001

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WHR	0.86±0.06	0.89±0.06	0.92±0.06	126.195	< 0.001	0.84±0.07	0.86±0.07	0.89±0.06	183.524	< 0.001
Fasting plasma glucose (mmol/L)	4.76 ± 1.08	4.98 ± 1.38	5.30 ± 1.94	24.275	< 0.001	4.65 ± 0.66	4.99 ± 1.26	5.31 ± 1.75	71.169	< 0.001
Total cholesterol (mmol/L)	4.73 ± 1.00	4.98 ± 1.06	5.17 ± 1.25	20.500	< 0.001	4.69 ± 0.94	4.98 ± 1.08	5.39 ± 0.98	73.075	< 0.001
Triglyceride (mmol/L)	1.54 ± 1.08	1.93 ± 1.94	2.38 ± 2.68	40.974	< 0.001	1.12 ± 0.64	1.54 ± 1.47	1.82 ± 1.40	90.583	< 0.001
Systolic blood pressure (mmHg)	110.52 ± 6.13	125.60 ± 6.54	145.64 ± 17.04	706.430	< 0.001	106.73 ± 8.21	125.23 ± 6.81	143.57± 20.48	755.356	< 0.001
Diastolic blood pressure (mmHg)	70.82 ± 5.79	80.27 ± 5.75	93.11 ± 10.66	592.747	< 0.001	68.84 ± 6.59	78.63 ± 6.19	89.20 ± 11.87	553.348	< 0.001
Family history of hypertension (%)				16.427	0.012				6.847	0.335
Only father	10.70	11.23	13.81			11.76	10.74	7.37		
Only mother	11.44	17.28	18.28			12.30	11.96	15.79		
Both parents	6.27	4.75	9.70			4.99	4.91	7.89		
Neither	71.59	66.74	58.21			70.94	72.39	68.95		
LAP	38.69 ± 34.85	58.43 ± 65.52	87.83 ± 120.94	113.508	< 0.001	24.52 ± 20.75	43.24 ± 59.48	58.98 ± 54.19	159.320	< 0.001

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1   BMI: body mass index; WC: waist circumference; WHR: waist-hip rate; LAP: lipid accumulation product.

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6   **Table 3** Comparison of blood pressure among four quartiles of LAP

Variables	LAP				Z	*P*-value
	Q1	Q2	Q3	Q4		
Male						
Systolic blood pressure (mmHg)	119.33 ± 13.72	125.61 ± 14.86	129.23 ± 16.38	133.36 ± 17.85	106.793	< 0.001
Diastolic blood pressure (mmHg)	75.84 ± 9.89	80.55 ± 9.84	82.56 ± 10.74	85.64 ± 11.36	106.285	< 0.001
Female						
Systolic blood pressure (mmHg)	110.45 ± 13.91	114.95 ± 15.07	119.66 ± 15.91	130.25 ± 19.78	184.926	< 0.001
Diastolic blood pressure (mmHg)	71.05 ± 9.45	73.29 ± 9.60	76.21 ± 9.96	81.04 ± 11.70	134.730	< 0.001

1

2 **Table 4** Multinomial logistic regression analysis of LAP associated with hypertension status

	OR[a](95% CI)		OR[b](95% CI)		OR[c](95% CI)	
Quartiles of LAP	prehypertension	hypertension	prehypertension	hypertension	prehypertension	hypertension
Male						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	2.98***	4.70***	2.22***	2.38**	1.73*	1.61
	(1.88, 4.72)	(2.34, 9.45)	(1.48, 3.34)	(1.36, 4.16)	(1.12, 2.67)	(0.89, 2.94)
Q3	4.48***	8.26***	2.68***	3.90***	1.66*	1.75
	(2.85, 7.03)	(4.21, 16.21)	(1.74, 4.12)	(2.24, 6.82)	(1.03, 2.68)	(0.94, 3.26)
Q4	4.65***	17.82***	3.14***	9.02***	1.67	2.79***
	(2.93, 7.36)	(9.21, 34.46)	(1.95, 5.07)	(5.11, 15.93)	(0.96, 2.92)	(1.43, 5.44)
Female						
Q1	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）	1（reference）
Q2	1.75**	2.19**	1.046	1.19	0.91	1.015
	(1.22, 2.51)	(1.27, 3.77)	(0.69,1.58)	(0.62,2.29)	(0.59,1.41)	(0.51,2.03)

Q3	3.35***	6.50***	1.68**	1.87	1.31	1.19
	(2.27, 4.93)	(3.83, 11.02)	(1.11,2.52)	(0.99,3.49)	(0.84,2.05)	(0.60,2.38)
Q4	5.99***	20.06***	3.26***	6.32***	2.10**	3.15***
	(3.74, 9.59)	(11.37, 35.38)	(2.09,5.10)	(3.42,11.65)	(1.26,3.51)	(1.56,6.39)

1   OR=Odds ratio; CI=confidence interval; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

2   [a], unadjusted.

3   [b], adjusted for age, sex, marital status, educational level

4   [c], adjusted for physical activity, smoker, drinker, BMI, WHR, fasting plasma glucose, family history of hypertension, and all the factors in b.

5

6   **Table 5** Predicting hypertension by different obesity indexes

Variables	Cut-off value	Sensitivity (%)	Specificity (%)	Youden Index	AUC(95% CI)	*P*-value
Male						
BMI	23.004	73.51	58.08	0.316	0.707 (0.672, 0.742)	< 0.001
WHR	0.906	58.58	70.27	0.289	0.688 (0.650, 0.725)	< 0.001
LAP	63.892	49.63	76.99	0.266	0.677 (0.640, 0.713)	< 0.001

WC	85.05	65.67	72.60	0.383	0.734 (0.700, 0.769)	< 0.001
TG	1.91	46.27	70.14	0.164	0.607 (0.568, 0.646)	< 0.001
Female						
BMI	21.767	81.58	50.73	0.323	0.698 (0.658, 0.737)	< 0.001
WHR	0.860	74.21	55.24	0.294	0.684 (0.643, 0.726)	< 0.001
LAP	30.860	68.95	67.42	0.363	0.721 (0.680, 0.761)	< 0.001
WC	79.90	72.11	64.94	0.370	0.725 (0.686, 0.766)	< 0.001
TG	1.26	63.68	64.49	0.282	0.663 (0.620, 0.706)	< 0.001

1 BMI: body mass index; WHR: waist-hip rate; LAP: lipid accumulation product; WC: waist circumference; TG: Triglyceride; AUC: area under curve;

2 OR=Odds ratio; CI=confidence interval.

3

4 **Table 6** Interaction effects between LAP and family history of hypertension

Variables	Variables	N	OR[c] (95% CI)	Interaction indexes (95% CI)
Male				
LAP[a]	Family history[b]			

32

-	-	486	1 (reference)	RERI = 1.652 (0.267, 3.037)[*]
-	+	215	1.189 (0.772, 1.832)	AP = 0.516 (0.238, 0.794)[*]
+	-	173	1.362 (0.875, 2.121)	SI = 3.998 (0.897, 17.820)
+	+	128	3.203[***] (2.002, 5.124)	

Female

LAP[a]	Family history[b]			
-	-	657	1 (reference)	RERI = -0.673 (-2.566, 1.220)
-	+	276	1.995[**] (1.284, 3.099)	AP = -0.328 (-1.451, 0.795)
+	-	108	1.729[*] (1.023, 2.922)	SI = 0.610 (0.125, 2.979)
+	+	36	2.051 (0.919, 4.589)	

1   LAP: lipid accumulation production; RERI: relative excess risk of interaction ; AP: attributable proportion due to interaction; SI: synergy index; OR=Odds

2   ratio; CI=confidence interval; [***], $P < 0.001$; [**], $P < 0.01$; [*], $P < 0.05$.

3   [a], grouped by the cut-off values in Table 4.

4   [b], family history of hypertension was defined as one parent or both parents having hypertension.

5   [c], adjusted for age, marital status, educational level, physical activity, smoker, drinker, BMI, and WHR.

Fig.1 The ROC curve of different obesity indexes in predicting hypertension in males.
legend
LAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference;
TG: Triglyceride.
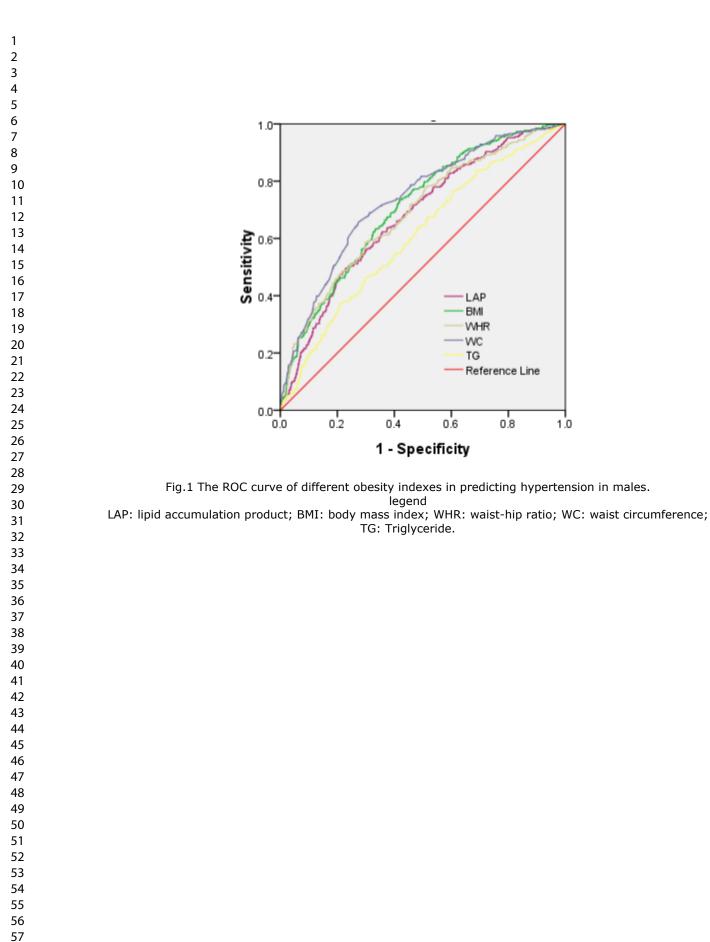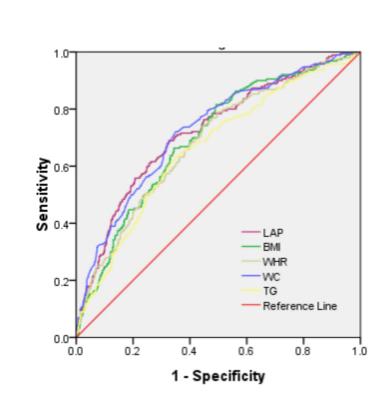
Fig.2 The ROC curve of different obesity indexes in predicting hypertension in females.legendLAP: lipid accumulation product; BMI: body mass index; WHR: waist-hip ratio; WC: waist circumference; TG: Triglyceride.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 3

Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7-8
		(*c*) Explain how missing data were addressed	Page 5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 5
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8-9; Table 1; Table 2
		(b) Give reasons for non-participation at each stage	Not application
		(c) Consider use of a flow diagram	Not application
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9; Table 1; Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Not application
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8-9; Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-10; Table 4; Table 6
		(*b*) Report category boundaries when continuous variables were categorized	Page 6-8; Table 1; Table 2; Table 3 ;

			Table 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not application
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11; Table 6
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.