

Original Article

Prevalence of metabolically healthy obesity and its impacts on incidences of hypertension, diabetes and the metabolic syndrome in Taiwan

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Obesity is an epidemic health problem related to morbidity and mortality of metabolic and cardiovascular diseases. However, little is known regarding the development of cardiometabolic diseases in an obese subgroup with a healthy metabolic risk profile. This study examined the prevalence of baseline metabolically healthy obese subjects and its impacts on the incidences of cardiometabolic diseases using a nation-wide population cohort. Metabolically healthy obese were prevalent in 8.2% of the baseline population and 28.5% of the obese subjects. Subjects included were 1,547 men and women (age range, 18–59 years), who were free of components of the metabolic syndrome except waist criteria. During an average 5.4-year follow-up, the cumulative incidences of hypertension, type 2 diabetes and the metabolic syndrome were 7.8%, 1.2% and 5.6%, respectively. The hazard ratios (95% CIs) for the metabolic syndrome incidence were significantly higher at BMI levels of ≥ 23.0 kg/m² [4.68 (2.22-9.86)] for BMI of 23-24.9 kg/m²; 8.82 (4.01-19.4) for BMI of 25-26.9 kg/m²; and 24.4 (12.3-48.4) for BMI of ≥ 27 kg/m². The hazard ratios for diabetes or hypertension incidence were significantly higher at BMI levels of ≥ 25.0 kg/m². Each kg/m² of BMI gained was associated with an 18% increase in the risk of developing hypertension and a 26% increase in risk for the metabolic syndrome. We conclude that metabolically healthy obese individuals are at higher risk to develop hypertension, type 2 diabetes and the metabolic syndrome than their non-obese counterparts. Our data provide further evidence that opposes the notion of metabolically healthy obese as harmless conditions.

Key Words: metabolically healthy obesity, type 2 diabetes mellitus, hypertension, the metabolic syndrome, incidence

INTRODUCTION

Obesity is an epidemic problem among Western populations and is also a growing health problem in the Taiwanese, an Asian population, with approximately one-third of the adult population classified as overweight or obese.¹ Obesity has increased healthcare costs and resulted in higher prevalence of and greater costs from cardiometabolic diseases,^{2,3} and also represents an onerous burden in terms of mortality in Taiwan.⁴

Although obesity is frequently associated with the metabolic disorders,^{5,6} not all obese individuals display a clustering of metabolic and cardiovascular risk factors. Recent interest has focused on an obese subgroup with a healthy metabolic profile despite increased adiposity and has been investigated by several researchers.^{7,8} Metabolically healthy obesity (MHO) describes the absence of any overt cardiometabolic disease and the absence of the metabolic syndrome components in an individual with a BMI ≥ 30 kg/m².⁹ Evidence suggests that MHO individuals may account for as much as 20-30% of the obese population.¹⁰⁻¹² Brochu¹³ and Karelis¹⁴ determined that MHO

individuals lack most of the metabolic abnormalities, display high levels of insulin sensitivity, a favorable lipid profile, and no sign of hypertension. In longitudinal studies, this phenotype was associated with reduced risks of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease.¹⁵

However, it is generally agreed that there is no evidence that these subjects are permanently protected from the risk of obesity-related co-morbidities. When compared with normal-body-weight controls, MHO subjects have higher risk of cardiovascular characteristics, such as carotid intima-media thickness¹⁶ and a deterioration of

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the endothelial function.¹⁷ Kuk *et al* showed that obese individuals, even in the absence of overt metabolic aberrations, are at higher risk of mortality than their non-obese counterparts.¹⁸

The prevalence of MHO on a population basis is not well established in Taiwan, and whether elevated body mass index (BMI) in the absence of overt metabolic aberrations confers risks for T2DM, hypertension and the metabolic syndrome is uncertain. In this study, we categorized subjects participated in a baseline survey into normal-weight, overweight, and obese BMI categories, who were all metabolically healthy individuals, to describe the community incidences of T2DM, hypertension and the metabolic syndrome to investigate the impacts of obesity and weight changes on these cardiometabolic diseases.

RESEARCH DESIGN AND METHODS

Data source

This study utilized data from the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia and Hyperlipidemia (TwSHHH). This nationwide epidemiological study was conducted in 2002 and followed up for 5.4 years (range, 4.9-6.1 years). The details of the TwSHHH baseline cohort were described previously¹.

Baseline examination

Subjects aged 18 to 59 years and metabolically healthy were included. Subjects were excluded if they had hypertension, T2DM, or history of stroke. Subjects were also excluded if they had any one of the components of the metabolic syndrome, except for the waist circumference criterion. The remaining 1,547 subjects (918 women and 629 men) were included in the analyses. The protocols for the TwSHHH were approved by the Institutional Review Board at the Bureau of Health Promotion, Department of Health, Executive Yuan, in Taiwan. All subjects gave written informed consent for participation.

Data collection

Data on sociodemographic characteristics including sex, age, exercise habit, alcohol drinking habit, smoking habit, family history of cardiovascular-related diseases and physician-diagnosed diseases were collected by trained public health nurses who administered a questionnaire during a home visit. During the visit, sitting blood pressure (BP), weight and height measurements were made. BMI was calculated as body weight (kg)/height² (m²). BMI cutoffs were adopted as suggested for Asians¹⁹ including normal weight (BMI: 18.5-22.9 kg/m²), overweight (BMI: 23-24.9 kg/m²) and obese 1 (BMI: 25-26.9 kg/m²) and obese 2 (BMI \geq 27 kg/m²) categories.

Follow-up data collection

The follow-up examination was conducted in 2007 (TwSHHH II). The collection of sociodemographic characteristics and anthropometric measurements were taken according to a standard protocol identical to that of the baseline examination. Written informed consent was provided by all study participants at the follow-up examination.

Diagnostic criteria for hypertension, T2DM and the metabolic syndrome incidence during follow-up period

Hypertension was defined if blood pressure was more than 140/90 mmHg or subjects were taking antihypertensive agents. Type 2 diabetes mellitus was defined according to the American Diabetes Association criteria. Medical history was reviewed and a diagnosis of incident diabetes was confirmed if the subject met any one of the following criteria: 1) fasting plasma glucose level of at least 7.0 mmol/L; 2) elevated HbA1C above 6.5%; and 3) treatment with antihyperglycemic medications. In this study, definition of the metabolic syndrome according to the modified AHA criteria²⁰ for Asians required meeting at least three of the following component risk factors: 1) waist circumference \geq 90 cm for men and \geq 80 cm for women; 2) triglycerides \geq 1.7 mmol/L; 3) HDL-C $<$ 1.0 mmol/L for men and $<$ 1.3 mmol/L for women; 4) systolic BP \geq 130 mmHg or diastolic BP \geq 85 mmHg or current use of antihypertensive drugs; and 5) fasting plasma glucose \geq 5.6 mmol/L or current use of antihyperglycemic agents.

Statistical analysis

SAS software (SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses. The demographic characteristics of subjects were compared between BMI categories via ANCOVA test for continuous variables for age adjustment, and differences in proportion data were assessed using the Cochran-Armitage trend test. Cumulative incidences of hypertension, T2DM and the metabolic syndrome were computed using the number of new cases over the follow-up period divided by the size of the population. Incidence rates were computed using the number of new cardiometabolic diseases cases divided by the follow-up person years. Cox's proportional-hazards models were used to derive the hazard ratios (HRs) and 95% CIs to determine the 5.4-year risk of overweight and obesity for developing hypertension, T2DM, and the metabolic syndrome. All models were adjusted for age, BMI change, exercise habit, alcohol drinking, smoking status and family history of T2DM and hypertension. The criteria for statistical significance were $p < 0.05$ and a 95% CI of HR that excluded 1.

RESULTS

Sample characteristics

The prevalence of MHO in 2002 accounted for 8.2% of 3,629 participants, aged 18-59 years, and 28.5% of the obese subjects. The prevalence of MHO was greater in women than in men (34.8% vs. 24.2%). Mean age of the cohort at baseline was 36.1 (10.8) (range 18-59) years, 59.3% were women and mean follow time was 5.4 (0.2) years. Characteristics of the study subjects divided by genders, stratified by BMI categories, are displayed in Table 1. Mean baseline BMI was 22.7 (3.0) kg/m². The distribution of the study population categorized according to the 2000 World Health Organization Asian Pacific Guideline is as follows: 61.6% of subjects were normal weight, 20.0% overweight (BMI, 23-24.9 kg/m²), 18.4% subjects were obese (BMI \geq 25 kg/m²). Of the subjects, 8.7% were obese according to the categories of classification of Department of Health in Taiwan (BMI \geq 27 kg/m²).

Table 1. Basic characteristics of the study sample aged 18-59 years and absence of the metabolic syndrome components except waist circumference criterion

Characteristics †‡	BMI categories (kg/m ²)				p [§]
	18.5-22.9	23-24.9	25-26.9	≥27	
Men	359 (57.1)	132 (21.0)	77 (12.2)	61 (9.7)	
Age (years)	32.1 (11.0)	38.9 (10.7)	38.7 (10.9)	36.6 (11.7)	<0.0001
BMI (kg/m ²)	21.0 (1.23)	24.0 (0.59)	25.9 (0.54)	29.4 (2.72)	<0.0001
Smoking habits-current smoker (%)	44.6	38.9	32.5	50.8	0.6906
Alcohol drinking habits (%)	15.3	18.9	24.7	18.0	0.1455
Exercise habits (%)	32.9	34.9	32.5	34.4	0.8393
Family history of hypertension	28.1	44.7	46.8	31.2	0.0210
Family history of T2DM	11.1	22.0	18.2	27.9	0.0003
Fasting plasma glucose (mmol/L)	4.66 (0.37)	4.83 (0.36)	4.82 (0.37)	4.85 (0.38)	<0.0001
Triglyceride (mmol/L)	0.97 (0.29)	1.06 (0.31)	1.18 (0.30)	1.20 (0.28)	<0.0001
HDL-C (mmol/L)	1.34 (0.27)	1.30 (0.22)	1.26 (0.22)	1.24 (0.20)	0.0074
Systolic blood pressure (mmHg)	108 (8.49)	108 (8.35)	110 (8.82)	113 (8.41)	0.0008
Diastolic blood pressure (mmHg)	70.7 (8.24)	73.0 (6.34)	73.6 (6.23)	75.5 (5.60)	<0.0001
Women	594 (64.7)	177 (19.3)	74 (8.1)	73 (8.0)	
Age (years)	35.6 (9.94)	39.4 (10.1)	40.8 (9.82)	39.4 (10.6)	<0.0001
BMI (kg/m ²)	20.7 (1.22)	23.9 (0.60)	25.9 (0.54)	29.7 (3.04)	<0.0001
Smoking habits-current smoker (%)	2.0	2.8	5.4	2.7	0.2259
Alcohol drinking habits (%)	2.7	1.7	6.8	0	0.7875
Exercise habits (%)	32.5	31.6	37.8	39.7	0.1873
Family history of hypertension	35.2	40.1	44.6	35.6	0.3035
Family history of T2DM	19.5	24.3	29.8	20.6	0.1735
Fasting plasma glucose (mmol/L)	4.71 (0.36)	4.82 (0.33)	4.87 (0.37)	4.78 (0.36)	<0.0001
Triglyceride (mmol/L)	0.90 (0.29)	0.91 (0.32)	0.96 (0.32)	0.97 (0.30)	0.0002
HDL-C (mmol/L)	1.54 (0.27)	1.50 (0.25)	1.42 (0.23)	1.38 (0.25)	<0.0001
Systolic blood pressure (mmHg)	102 (9.68)	104 (10.5)	105 (9.24)	109 (8.65)	<0.0001
Diastolic blood pressure (mmHg)	67.2 (7.66)	69.1 (7.48)	70.0 (7.67)	71.5 (7.41)	<0.0001

† Values for continuous characteristics were expressed as mean (SD).

‡ T2DM, type 2 diabetes mellitus; HDL-C, high-density lipoprotein cholesterol.

§ p values using Cochran-Armitage trend test for categorical data and using age-adjusted general linear model for continuous variables.

Table 2. Multiple variables-adjusted hazard ratios for occurrence of cardiometabolic diseases by categories of baseline BMI and its changes

	Baseline BMI categories (kg/m ²)				BMI changes
	18.5-22.9	23-24.9	25-26.9	≥27	
	HR [‡] (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total					
Metabolic syndrome	1.0 (reference)	4.68 (2.22-9.86)	8.82 (4.01-19.4)	24.4 (12.3-48.4)	1.26 (1.17-1.36)
Hypertension	1.0 (reference)	1.45 (0.89-2.36)	2.72 (1.60-4.62)	4.25 (2.64-6.84)	1.18 (1.09-1.28)
T2DM [†]	1.0 (reference)	1.71 (0.38-7.73)	5.03 (1.23-20.5)	11.5 (3.38-39.1)	1.08 (0.87-1.34)
Men					
Metabolic syndrome	1.0 (reference)	6.01 (1.64-21.92)	14.77 (3.61-60.3)	25.1 (7.26-86.8)	1.64 (1.36-1.99)
Hypertension	1.0 (reference)	1.16 (0.59-2.27)	1.50 (0.64-3.50)	3.69 (1.93-7.07)	1.19 (1.04-1.36)
T2DM	1.0 (reference)	2.80 (0.23-33.48)	4.23 (0.25-72.3)	14.3 (1.21-168)	1.24 (0.72-2.13)
Women					
Metabolic syndrome	1.0 (reference)	5.08 (1.98-13.07)	8.80 (3.12-24.8)	29.54 (12.6-69.3)	1.20 (1.09-1.32)
Hypertension	1.0 (reference)	2.34 (1.09-5.02)	5.18 (2.41-11.2)	6.23 (2.88-13.4)	1.15 (1.03-1.28)
T2DM	1.0 (reference)	0.87 (0.09-8.55)	5.56 (1.09-28.3)	14.6 (3.23-65.5)	1.07 (0.83-1.38)

† T2DM, type 2 diabetes mellitus;

‡ Cox regression model: adjusted for age, smoking status, alcohol intake status, exercise, family history of diabetes or hypertension.

Among 1,547 participants aged 18-59 years at study entry (in 2002), 7.8% of the subjects had developed hypertension and 1.2% of subjects developed T2DM during mean 5.4 years of follow-up. In addition, 5.6% of subjects developed the metabolic syndrome. There were higher incidences of hypertension, T2DM, and the metabolic syndrome in the higher BMI categories, with significant p-value for trend test (Figure 1).

In Cox models, adjusted HRs of the metabolic syndrome significantly increased at BMI levels ≥ 23.0 kg/m²

(Table 2). The HRs (95% CI) of developing the metabolic syndrome were 4.68 (2.22-9.86) for baseline BMI 23-24.9 kg/m² relative to normal BMI 18.5-22.9 kg/m², increasing to 8.82 (4.01-19.4) for BMI 25-26.9 kg/m², and 24.4 (12.3-48.4) for BMI ≥ 27 kg/m² and showed similar trends among both genders. The HRs of developing hypertension were statistically significant starting at the BMI category of 23-24.9 kg/m² in women, but only significant at BMI ≥ 27 kg/m² in men. The risk for developing T2DM increased progressively with increasing categories of

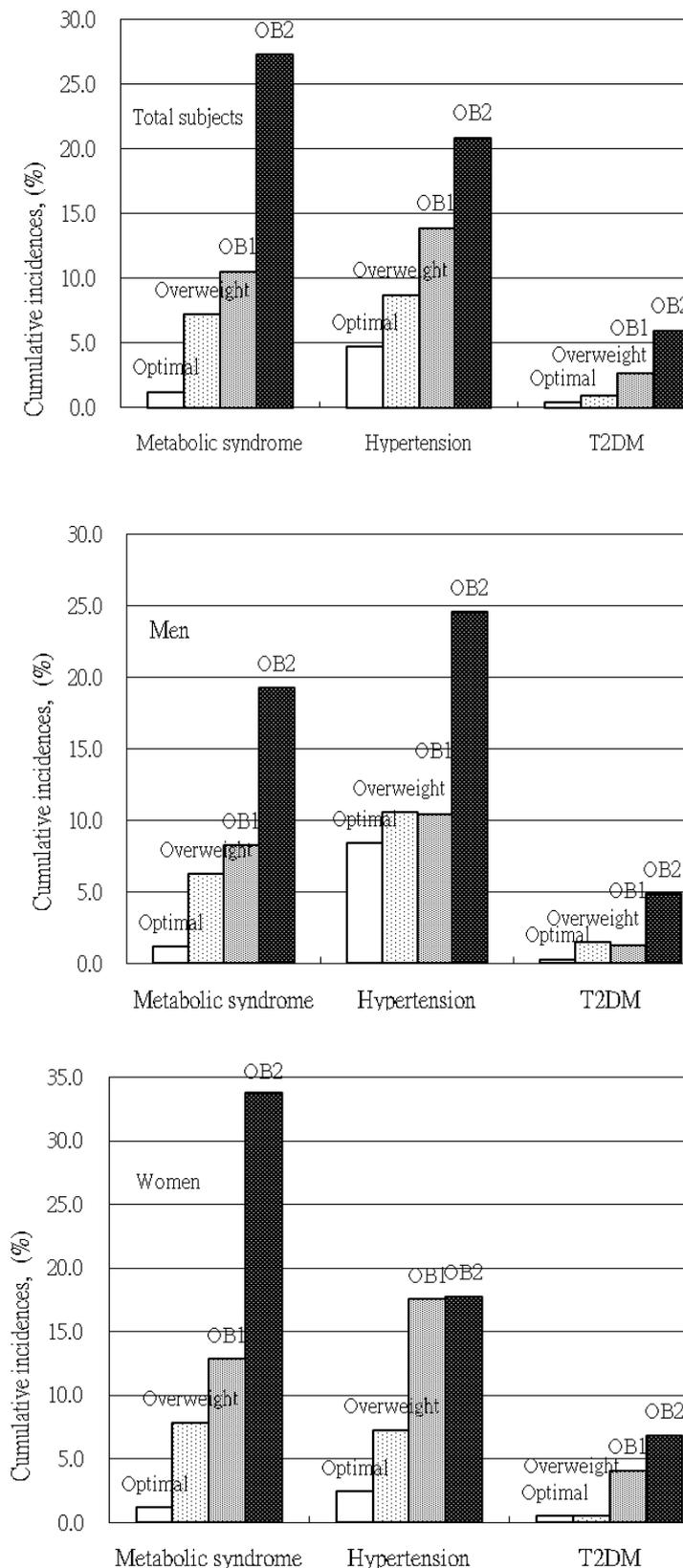


Figure 1. Cumulative incidences of cardiometabolic diseases according to BMI (kg/m²) categories. OB1, BMI: 25-26.9 kg/ m²; OB2, BMI ≥27 kg/ m².

baseline BMI, and HRs significantly increased at BMI levels more than 25.0 kg/m² (Table 2).

Weight gain was strongly related to the risk of cardiometabolic diseases. Each kg/ m² of BMI gain was associated with a 18% increase in the risk of developing hy-

pertension and a 26% increase in the risk of developing the metabolic syndrome.

DISCUSSIONS

This analysis suggests that MHO is not so rare in Taiwan,

accounting for 28.5% of obese subjects and 8.2% of the middle-aged Asian population. Moreover, MHO individuals are at higher risk to develop hypertension, T2DM and the metabolic syndrome than their non-obese counterparts. Thus, our data provide further evidence that opposes the notion of MHO as harmless conditions.

To date, there is no uniform definition for MHO. Due to the absence of harmonized criteria,⁹ previous studies report MHO subjects to be 20-30% of obese subjects depending on the definition.¹⁰⁻¹² Insulin sensitivity could be the key factor discriminating healthy from at-risk obese subjects.²¹ Using different criteria, 16.6-31.7% of obese US adults showed a metabolic healthy profile in the National Health and Nutrition Examination Surveys (NHANES 1999–2004).²² We used a more stringent definition for MHO subjects of those with no criteria for the metabolic syndrome (exception for waist circumference) and indicated that the prevalence of MHO in obese middle aged subjects was nearly one-fourth in men and one-third in women.

The existence of a subset of obese subjects is an indubitable fact, but whether this protection is represented permanently or this is just a step to evolving risk factors and, then, of overt cardiometabolic diseases, is unknown. It has been reported that MHO subjects display high levels of insulin sensitivity, normal lipid and blood pressure profile and no inflammation profiles.^{13,14,23} Hayes *et al* showed that MHO women had lower intra-abdominal fat volume and less insulin resistance than those with an abnormality.²⁴ Brochu *et al*¹³ identified a subgroup of MHO postmenopausal women who were insulin-sensitive. The protective metabolic profile observed in MHO individuals was associated with lower incidences of T2DM.¹⁵ Moreover, Karelis *et al* investigated the effect of a 6 month energy-restricted diet on insulin sensitivity and showed this had decreased by 13% in MHO individuals.²⁵

In contrast with these findings, it has been reported that MHO still has higher risk of cardiometabolic diseases and some reports seem to confirm this hypothesis. In large-scale longitudinal studies for Caucasian populations, the association between MHO and further morbidity and mortality were investigated. In an 11-year follow-up study,¹⁵ Meigs *et al* demonstrated that MHO was associated with a 3- to 4-fold risk for T2DM or cardiovascular disease events, accounting for 2-3% of these events in the population.¹⁵ Similar results have been obtained in the Janssen *et al*²⁶ study, in which it was demonstrated that MHO has a significant impact on the appearance of diabetes, dyslipidemia and hypertension for a 10-year follow-up duration. Kuk *et al*¹⁸ demonstrated a significantly increased risk of all causes of mortality associated with MHO. Arnlo *et al* revealed that MHO should be considered a harmful condition related to T2DM incidence²⁷ and imputed increased risk for cardiovascular events and total mortality during 30 years of follow-up²⁸.

In our study, the cumulative incidence of hypertension increased from 4.7% in normal-body-weight subjects to 8.7% in overweight subjects, 13.9% in mild-obese subjects and 20.9% in subjects with BMI higher than 27 kg/m²; thus suggesting that increasing BMI drastically increased the chances of being hypertensive. Similar results were obtained for T2DM and the metabolic syn-

drome. Although obesity accounts for 18.4% of the population, nearly 60% of subjects with T2DM or the metabolic syndrome are obese. In addition to BMI, weight gain appeared to precede the onset of cardiometabolic diseases. Our finding showed that the existence of MHO does not necessarily represent permanently low risk, and moreover, weight gain increase risk. Pan *et al* observed the diet and health trends in Taiwan, and revealed that energy intakes have increased combined with an increasingly sedentary lifestyle.²⁹ These trends are related to the increase in obesity.

Limitation

In addition to overt pathologies, to categorize subjects as metabolically normal or abnormal can be defined by using HOMA index, the metabolic syndrome components or inflammatory markers.⁹ No data of serum insulin or hs-C-reactive protein (CRP) for further exclusion of metabolically abnormality in our study was a limitation of research; therefore we adopted a metabolic syndrome criterion to exclude subjects with insulin resistant characters. It is rare to be insulin-resistant while subject's blood glucose levels were less than 5.6 mmol/L, triglyceride <1.7 mmol/L, HDL-C \geq 1.0 mmol/L in men, \geq 1.3 mmol/L in women and blood pressure <130/85 mmHg.

Conclusion

Results of the present study indicate that obesity in the absence of the metabolic abnormalities is not such a rare condition in Taiwan. Furthermore, obesity and weight gain are associated with an increased risk for incidences of hypertension, T2DM and the metabolic syndrome in the metabolically healthy, middle-aged population. As such, weight management should continue to be a target for reducing cardiometabolic diseases in all obese individuals.

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AUTHOR DISCLOSURES

The authors declare that there is no duality of interest associated with this manuscript.

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正常代謝水準之肥胖狀態在臺灣之盛行率及其對於高血壓、糖尿病和代謝症候群發生率的影響

肥胖是與代謝疾病和心臟血管疾病罹病率及死亡率密切相關之流行性健康問題。然而，對於具有正常代謝水準之肥胖狀態，其罹患代謝疾病和心臟血管疾病的危險性所知有限。本研究是以具有全國代表性之研究世代為研究個案，探討具有正常代謝水準之肥胖狀態盛行率及其對於代謝疾病和心臟血管疾病發生率的影響。納入分析之研究個案數為 1,547 人(年齡介於 18-59 歲)。這些納入分析的研究個案在基礎收案時，除了腰圍一項外，並未具有代謝症候群之其他危險因子。研究結果發現，在此一研究世代族群中，具有正常代謝水準而肥胖之盛行率為 8.2%；而在肥胖族群中具有正常代謝水準之比率為 28.5%。在平均 5.4 年的追蹤過程中，研究世代之高血壓、第二型糖尿病及代謝症候群之累積發生率分別為 7.8%、1.2%及 5.6%。罹患代謝症候群之相對危險性隨著身體質量指數的增加而顯著的增加：相對於身體質量指數為 18.5-22.9 kg/m²，身體質量指數為 23.0-24.9 kg/m² 者之相對危險性為 4.68 (95%信賴區間為 2.22-9.86)；身體質量指數為 25.0-26.9 kg/m² 者之相對危險性為 8.82 (95%信賴區間：4.01-19.4)；身體質量指數 ≥27.0 kg/m² 者之相對危險性為 24.4 (95%信賴區間：12.3-48.4)。同時，身體質量指數每增加 1 kg/m²，罹患高血壓的危險性提高了 18%，而罹患代謝症候群之危險性增加 26%。本研究結果顯示，具正常代謝水準之肥胖狀態仍有罹患高血壓、第二型糖尿病及代謝症候群的高危險性。本研究結果並不支持具有正常代謝水準之肥胖狀態為一無健康危害狀態的論點。

關鍵字：正常代謝水準的肥胖、第二型糖尿病、高血壓、代謝症候群、發生率