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임상의과학 석사 학위논문

대사적으로 건강한 비만에서
뇌경색 위험 고찰

**Risk of ischemic stroke in
metabolically healthy obesity:
a nationwide population-based study**

2018 년 2 월

서울대학교 대학원

의과대학 임상과학과

이 현 정

1 대사적으로 건강한 비만에서

2 뇌경색 위험 고찰

3 **Risk of ischemic stroke in metabolically healthy**
4 **obesity: a nationwide population-based study**

5
6 지도교수 김 용 진

7 이 논문을 임상의과학 석사 학위논문으로 제출함

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1 **Abstract**

2 **Risk of ischemic stroke in**
3 **metabolically healthy obesity:**
4 **a nationwide population-based study**

5

6

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11 **Background**

12 Whether metabolically healthy obese (MHO) individuals are at increased risk of
13 ischemic stroke is not well known. We investigated the association of the MHO
14 phenotype with ischemic stroke.

15 **Methods**

16 A total of 354,083 adults (age 45.8 ± 14.2 years) from the Korean National Health
17 Insurance Service–National Sample Cohort enrolled in 2004–2008 were followed-up
18 for incident ischemic stroke until 2013. Obesity was defined as body mass index
19 (BMI) ≥ 25 kg/m². Subjects meeting none of the metabolic syndrome criteria were
20 classified as ‘metabolically healthy’. The cohort was categorized into four groups
21 according to obesity and metabolic status: metabolically healthy non-obese (MHNO),
22 metabolically unhealthy non-obese (MUNO), MHO, and metabolically unhealthy
23 obese (MUO).

1 **Results**

2 Ischemic stroke was newly diagnosed in 4,884 (1.4%) individuals during a mean
3 follow-up of 7.4 ± 1.5 years. While higher BMI was associated with a significantly
4 increased risk for stroke, the effect of BMI differed according to metabolic health
5 status. In metabolically healthy individuals, obesity did not increase the risk for
6 ischemic stroke, regardless of the severity of obesity. Meanwhile, in metabolically
7 unhealthy individuals, being obese was significantly associated with increased risk
8 of stroke. Stroke incidence rates for the MHNO, MUNO, MHO, and MUO groups
9 were 0.56, 2.61, 0.61, and 2.76 per 1,000 person-years, respectively. Risk for stroke
10 increased significantly in metabolically unhealthy groups, but it was not increased
11 in MHO compared to the MHNO group on multivariate analysis.

12 **Conclusions**

13 MHO individuals were not at increased risk for ischemic stroke. However, obesity
14 increased risk for ischemic stroke in persons with metabolic risk factors; therefore,
15 maintaining normal weight may be more important for this population. Also,
16 metabolic unhealthiness showed greater association than obesity with stroke.

17
18
19 Keywords: Obesity, metabolic syndrome, metabolically healthy obesity, ischemic
20 stroke, epidemiology, Korean National Health Insurance Service

21 Student Number: 2016-22231

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1 **Introduction**

2 Obesity and metabolic syndrome, often co-existing, are associated with increased
3 cardiovascular risk and poor health outcomes. However, a subset of obese
4 individuals with an otherwise metabolically healthy profile, termed the
5 ‘metabolically healthy obese (MHO)’, may have a better cardiovascular prognosis
6 compared to the rest of the obese population. Defining ‘metabolically healthy’ is a
7 matter of debate, and depending on studies, having 0 or up to 1 metabolic syndrome
8 risk factor is the commonly used definition.

9 Stroke is a major health burden despite decreasing mortality[1]. Known risk factors
10 for stroke include non-modifiable factors such as age, low birth weight, ethnicity,
11 genetic factors, while modifiable factors include hypertension, diabetes mellitus,
12 dyslipidemia (total cholesterol), obesity and body fat distribution, physical inactivity,
13 diet (high-salt, low potassium), smoking, and atrial fibrillation[2]. Stroke is often
14 considered as part of a composite cardiovascular outcome with coronary heart
15 disease; however, cardiovascular risk may differ according which component
16 outcome, such as myocardial infarction or stroke, is being examined. Some previous
17 studies have found MHO to be at increased cardiovascular risk (including stroke)[3-
18 5], while others have found no difference in risk between the MHO and MHNO
19 phenotypes[6-9]. Even when examining stroke alone as the primary outcome, there
20 were conflicting data that stroke risk was increased[3] and not increased[6, 7] in
21 MHO.

22 We examined the risk for ischemic stroke associated with obesity and metabolic
23 health status, using a strict definition for being metabolic healthy, in a nationwide
24 population-based cohort.

25
26

1 **Materials and methods**

2 **Study population**

3 The Korean National Health Insurance Service–National Sample Cohort (NHIS-
4 NSC) consists of 1,025,340 randomly selected subjects from the general Korean
5 population in 2002 (2.2% of the total Korean population) and their follow-up data
6 until December 2013. Details of this database representing the general Korean
7 population have been previously described[10, 11]. Demographics, medical
8 treatment records of inpatient and outpatient care such as diagnoses, prescriptions,
9 and procedures, and nationwide health examination results were available for
10 research.

11 From the NHIS-NSC, a retrospective cohort of Korean adults (age > 20 years), who
12 had undergone a baseline health examination including body mass index (BMI) from
13 2004 to 2008 and did not have a prior diagnosis of ischemic stroke, was extracted (n
14 = 370,537). Those with a previous diagnosis of ischemic stroke (I63-64) during the
15 past 3 years were excluded, because previous diagnostic coding of stroke in the
16 NHIS claims database could not be differentiated from new-onset stroke.
17 Underweight individuals (BMI < 18.5 kg/m²) were also excluded (n = 16,454). A
18 total of 354,083 were included in the final study cohort.

19 Diagnoses were defined by the International Classification of Diseases, 10th revision
20 (ICD-10). This study was approved by the Seoul National University Hospital
21 Institutional Review Board, and adhered to the Declaration of Helsinki.

22

23 **Definitions of obesity and metabolic health**

24 Obesity was ascertained by BMI. BMI was calculated by dividing weight in
25 kilograms by the square of height in meters (kg/m²) and categorized using the WHO

1 Western Pacific Region definition of obesity for Asians[12]: non-obese (BMI 18.5-
2 24.9 kg/m²) and obese (BMI ≥ 25 kg/m²), with non-obese being further classified as
3 normal weight (BMI 18.5-22.9 kg/m²) and overweight (BMI 23.0-24.9 kg/m²), and
4 obesity being further classified as stage I (BMI 25-29.9 kg/m²) and stage II (BMI ≥
5 30 kg/m²). As previously mentioned, underweight individuals (BMI < 18.5 kg/m²)
6 were excluded from the study.

7 Metabolic health status was ascertained using metabolic syndrome criteria[13]. As
8 only total cholesterol levels were measured at baseline health examinations before
9 2009, neither triglycerides nor high-density lipoprotein-cholesterol (HDL) levels
10 were available; thus, we used elevated total cholesterol levels of ≥ 240 mg/dL as a
11 proxy indicator of abnormal lipid levels, which is the cut-off for high cholesterol
12 levels according to NCEP-ATPIII and Korean guidelines[14, 15]. In concordance to
13 a recently proposed harmonized definition of MHO[16], being metabolically healthy
14 was defined as meeting none of the following metabolic syndrome criteria at baseline:
15 i) elevated blood pressure (SBP ≥ 130 and/or DBP ≥ 85 mmHg) or treatment for
16 hypertension, ii) elevated fasting glucose (≥ 100 mg/dL) or treatment for diabetes
17 mellitus, iii) elevated total cholesterol (≥ 240 mg/dL) or treatment for dyslipidemia.
18 Individuals who met one or more of the above criteria were considered metabolically
19 unhealthy. The waist circumference criterion was excluded. Treatment for
20 hypertension, type 2 diabetes mellitus, dyslipidemia were ascertained using
21 diagnosis codes during the past year with record of hospitalization or outpatient visit
22 (S1 Table).

23 The cohort was categorized into four groups according to obesity and metabolic
24 status: metabolically healthy non-obese (MHNO), metabolically unhealthy non-
25 obese (MUNO), MHO, and metabolically unhealthy obese (MUO).

26

1 **Endpoint**

2 The primary endpoint was newly diagnosed ischemic stroke. This variable was
3 defined as diagnosis of ischemic stroke (I63-64) given during hospitalization
4 combined with claims for neurologic imaging by computed tomography or magnetic
5 resonance. Patients who did not develop ischemic stroke during the follow-up period
6 were censored on the day of drop-out (due to death or emigration) or at the end of
7 follow-up.

8

9 **Covariates**

10 Multivariate adjustments were made for sex, age, income (lower 20 percentile, upper
11 80 percentile), area (urban, rural), smoking status (non-smoker, ex-smoker, current
12 smoker), alcohol intake (none, 1–3 times/month, ≥ 1 time/week), exercise status
13 (none, 1–4 times/week, ≥ 5 times/week), and comorbidities. Demographic data were
14 obtained by questionnaires at baseline health examinations. Comorbidities were
15 defined by ICD-10 diagnoses codes during the past year with record of
16 hospitalization or outpatient clinic treatments. Definitions of covariates were
17 validated in our previous studies[10, 17, 18], and are summarized in **Supplementary**
18 **Table 1**. Components of CHA2DS2-VASc score such as ischemic heart disease,
19 peripheral artery disease, congestive heart failure, transient ischemic attack, venous
20 thromboembolism, as well as chronic obstructive pulmonary disease, end-stage renal
21 disease, liver cirrhosis, cancer, and history of cardiac surgery were adjusted for.

22

23 **Statistical analysis**

24 The characteristics of the cohort are presented as means \pm standard deviation (SD)
25 for continuous variables and percentage for categorical variables. Differences

1 between groups were tested by analysis of variance (ANOVA) for continuous
2 variables and chi-square test for categorical variables.

3 Incidence rates were calculated per 1,000 person-years. The cumulative incidence of
4 ischemic stroke for each group was plotted with Kaplan-Meier curves and compared
5 by the log-rank test. Cox proportional hazard models were used to assess the risk of
6 ischemic stroke. Time was defined as days from inclusion to either incident ischemic
7 stroke or censoring due to death, emigration, or end of follow-up. Stroke risk was
8 expressed as the hazard ratio (HR) with 95% confidence interval (95%CI). The
9 significance level was set at two-sided $p < 0.05$. All statistical analyses were
10 performed using SPSS version 22 and SAS version 9.2 (SAS Institute, Cary, NC,
11 USA).

12
13

14 **Results**

15 **Baseline characteristics of the study population**

16 The baseline characteristics of the study population are summarized in **Table 1**. The
17 biggest portion was normal weight (43.0%), and 31.9% of the participants were
18 obese, though only 3.2% had $BMI \geq 30 \text{ kg/m}^2$ (**Figure 1**). More than half (61.3%)
19 were metabolically unhealthy. Participants were categorized into four groups
20 according to obesity and metabolic health status: MHNO (31.2%), MUNO (36.9%),
21 MHO (7.5%), and MUO (24.4%). The groups showed significant differences in all
22 baseline characteristics. Metabolically unhealthy groups tended to be older. The
23 obese groups showed higher proportion of men. Metabolically unhealthy groups had
24 higher rates of comorbidities compared to metabolically healthy groups. The MUO
25 tended to have more metabolic risk factors compared to the MUNO.

26

1 **Table 1. Baseline characteristics of the study population**

	Total (n=354,083)	MHNO (n=110,531, , 31.2%)	MUNO (n=130,583, , 36.9%)	MHO (n=26,448, 7.5%)	MUO (n=86,521, 24.4%)
Male sex, n (%)	186,563 (52.7%)	46,599 (42.2%)	72,758 (55.7%)	15,395 (58.2%)	51,811 (59.9%)
Age, years	45.8 ± 14.2	39.1 ± 12.2	49.7 ± 14.5	41.7 ± 11.7	49.8 ± 13.4
Body mass index, kg/m ²	23.8 ± 3.0	21.8 ± 1.7	22.5 ± 1.6	26.9 ± 1.8	27.4 ± 2.2
Elevated blood pressure*	146,622 (41.4%)		83,920 (64.3%)		62,702 (72.5%)
Elevated fasting glucose†	98,735 (27.9%)		58,419 (44.7%)		40,316 (46.6%)
Elevated total cholesterol‡	37,790 (10.7%)		20,514 (15.7%)		17,276 (20.0%)
Hypertension	52,487 (14.8%)		26,852 (20.6%)		25,635 (29.6%)
Diabetes mellitus	16,332 (4.6%)		8,590 (6.6%)		7,742 (8.9%)
Dyslipidemia	34,116 (9.6%)		18,613 (14.3%)		15,503 (17.9%)
Ischemic heart disease	10,246 (2.9%)	488 (0.4%)	5,069 (3.9%)	167 (0.6%)	4,522 (5.2%)
Peripheral artery disease	8,421 (2.4%)	555 (0.5%)	4,203 (3.2%)	181 (0.7%)	3,482 (4.0%)
Congestive heart failure	4,635 (1.3%)	392 (0.4%)	2,144 (1.6%)	135 (0.5%)	1,964 (2.3%)
Transient ischemic attack	1,435 (0.4%)	133 (0.1%)	663 (0.5%)	43 (0.2%)	596 (0.7%)
Venous thromboembolism	63 (0.0%)	5 (0.0%)	34 (0.0%)	4 (0.0%)	20 (0.0%)
End-stage renal disease	109 (0.0%)	5 (0.0%)	77 (0.1%)	0 (0.0%)	27 (0.0%)
Liver cirrhosis	754 (0.2%)	102 (0.1%)	399 (0.3%)	41 (0.2%)	212 (0.2%)
Chronic obstructive pulmonary disease	18,744 (5.3%)	4,042 (3.7%)	8,337 (6.4%)	980 (3.7%)	5,415 (6.3%)

Cancer	4,757 (1.3%)	965 (0.9%)	2,243 (1.7%)	233 (0.9%)	1,316 (1.6%)
Cardiac surgery	157 (0.0%)	9 (0.0%)	98 (0.1%)	3 (0.0%)	47 (0.1%)
Smoking					
Non-smoker	241,159 (68.1%)	79,800 (72.2%)	87,556 (67.1%)	16,871 (63.8%)	56,932 (65.8%)
Ex-smoker	18,470 (5.2%)	4,354 (3.9%)	7,058 (5.4%)	1,457 (5.5%)	5,601 (6.5%)
Current-smoker	94,454 (26.7%)	26,377 (23.9%)	35,969 (27.5%)	8,120 (30.7%)	23,988 (27.7%)
Drinking					
Non-drinker	185,788 (52.5%)	57,771 (52.3%)	70,104 (53.7%)	13,009 (49.2%)	44,904 (51.9%)
2-3 times per month	65,693 (18.6%)	25,528 (23.1%)	21,000 (16.1%)	5,545 (21.0%)	13,620 (15.7%)
≥ 1 time per week	102,602 (29.0%)	27,232 (24.6%)	39,479 (30.2%)	7,894 (29.8%)	27,997 (32.4%)
Exercise					
None	193,463 (54.6%)	63,808 (57.7%)	71,533 (54.8%)	13,494 (51.0%)	44,628 (51.6%)
1-4 times per week	131,245 (37.1%)	39,896 (36.1%)	46,766 (35.8%)	10,965 (41.5%)	33,618 (38.9%)
≥ 5 times per week	29,375 (8.3%)	6,827 (6.2%)	12,284 (9.4%)	1,989 (7.5%)	8,275 (9.6%)
Low income (Lowest 20 percentile)	54,983 (15.5%)	17,313 (15.7%)	20,951 (16.0%)	3,867 (14.6%)	12,852 (14.9%)
Rural area	190,202 (53.7%)	57,071 (51.6%)	71,154 (54.5%)	14,265 (53.9%)	47,712 (55.1%)
Obesity	112,969 (31.9%)				
BMI 25-29.9 kg/m ²	101,657 (28.7%)			24,861 (94.0%)	76,796 (88.8%)
BMI ≥ 30 kg/m ²	11,312 (3.2%)			1,587 (6.0%)	9,725 (11.2%)
Metabolically unhealthy	217,104 (61.3%)				
Number of MetS criteria					
1			83,399 (63.9%)		44,091 (51.0%)

2			38,102 (29.2%)		31,576 (36.5%)
3			9,082 (7.0%)		10,854 (12.5%)
Mean follow-up duration, years	7.43 ± 1.52	7.45 ± 1.48	7.44 ± 1.54	7.45 ± 1.48	7.38 ± 1.55

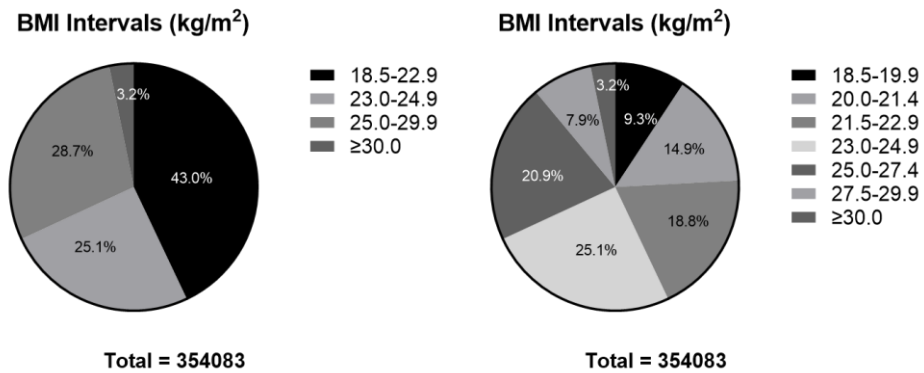
1 MetS = metabolic syndrome

2 * SBP ≥ 130 and/or DBP ≥ 85 mmHg; † Fasting glucose ≥ 100 mg/dL; ‡ Total cholesterol ≥ 240

3 mg/dL

4

Figure 1



5

6 **Figure 1. Fractions of BMI intervals.**

7

8 **Risk of stroke according to BMI and number of metabolic risk**

9 **factors**

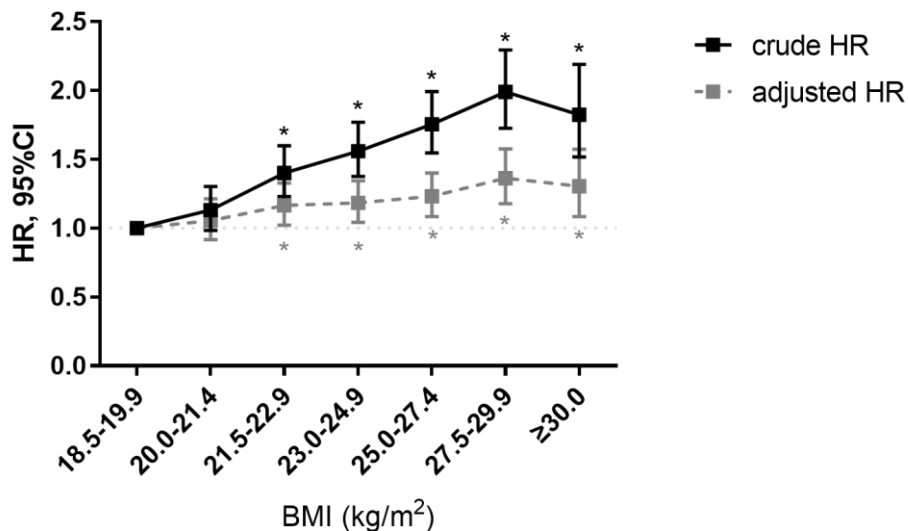
10 **Table 2** presents the association of obesity, metabolic health components, and
 11 metabolic health status with ischemic stroke. Compared to non-obese individuals,
 12 obese individuals had 16% increased risk of ischemic stroke (HR 1.16, 95%CI 1.09-
 13 1.23), which was significant after adjustment for other metabolic syndrome criteria,
 14 i.e. elevated blood pressure, glucose, or cholesterol levels (**Table 2, Model 2**).

1 Overweight individuals also showed 8% increased risk for stroke. The association
2 with stroke became stronger with increasing BMI, though the association was much
3 attenuated after adjustment for metabolic health components (**Figure 2**). The number
4 of metabolic syndrome risk factors increased in proportion to higher BMI interval
5 (**Figure 3**).

6 All components of metabolic syndrome criteria were associated with incident stroke
7 as well, which was significant after adjustment for obesity (**Table 2**, Model 3).
8 Elevated blood pressure showed the strongest association with stroke development
9 (HR 1.74, 95%CI 1.62-1.86). Compared with metabolically healthy individuals,
10 metabolically unhealthy individuals had an 80% increased risk for ischemic stroke
11 with adjustment for obesity (HR 1.80, 95%CI 1.65-1.97). Overall, the presence of
12 each metabolic syndrome criteria or metabolic unhealthiness showed stronger
13 association with ischemic stroke than obesity status.

14

Figure 2

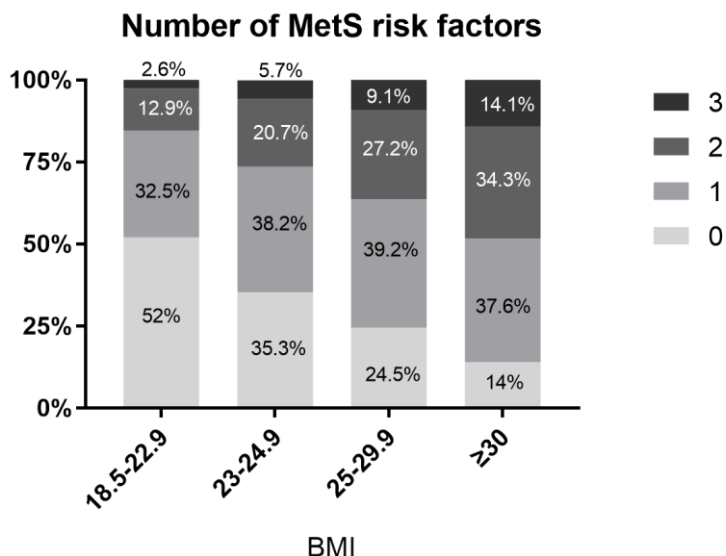


15

16 **Figure 2. Risk for ischemic stroke according to BMI.**

- 1 Each point representing hazard ratios (HRs) with error bars for 95% confidence intervals (95% CI).
- 2 Asterisks indicated significant difference with reference group.
- 3

Figure 3



4
5 **Figure 3. Number of metabolic syndrome risk factors according to BMI**
6 **intervals.**

7
8 **Table 2. The association of obesity, metabolic health components, and metabolic**
9 **health status with ischemic stroke**

	N	Stroke cases	Model 1 [†] HR (95% CI)	Model 2 [‡] HR (95% CI)	Model 3 [§] HR (95% CI)
Obesity					
Non-obese	241,114	3,000 (1.2%)	1 (ref)	1 (ref)	
Obese	112,969	1,884 (1.7%)	1.25 (1.18-1.32)	1.16 (1.09-1.23)	
BMI intervals					

BMI 18.5-22.9 kg/m ² (Normal weight)	152,101	1,715 (1.1%)	1 (ref)	1 (ref)
BMI 23.0-24.9 kg/m ² (Overweight)	89,013	1,285 (1.4%)	1.16 (1.08-1.25)	1.08 (1.01-1.16)
BMI 25-29.9 kg/m ² (Stage I obesity)	101,657	1,700 (1.7%)	1.32 (1.23-1.41)	1.15 (1.08-1.24)
BMI ≥ 30 kg/m ² (Stage II obesity)	11,312	184 (1.6%)	1.46 (1.25-1.70)	1.19 (1.02-1.38)
Metabolic health components (MetS criteria)				
Elevated blood pressure or treatment for hypertension	161,450	3,784 (2.3%)	1.78 (1.66-1.91)	1.74 (1.62-1.86)
Elevated glucose or treatment for diabetes mellitus	101,374	2,314 (2.3%)	1.25 (1.18-1.33)	1.24 (1.17-1.32)
Elevated total cholesterol or treatment for dyslipidemia	63,830	1,567 (2.5%)	1.23 (1.15-1.31)	1.22 (1.14-1.30)
Metabolic health status				
Healthy (0 MetS criteria)	136,979	586 (0.4%)	1 (ref)	1.0 (ref)
Unhealthy (≥1 MetS criteria)	217,104	4,884 (1.4%)	1.86 (1.70-2.03)	1.80 (1.65-1.97)

1 HR = Hazard ratio; CI = Confidence interval; BMI = body mass index; MetS = metabolic syndrome

1 † Adjusted for age, sex, income, area, smoking, drinking, exercise, history of ischemic heart disease,
 2 peripheral artery disease, congestive heart failure, transient ischemic attack, venous
 3 thromboembolism, chronic obstructive pulmonary disease, end-stage renal disease, liver cirrhosis,
 4 cancer, and cardiac surgery; ‡ Further adjustment for metabolic health components; § Further
 5 adjustment for obesity

6
 7 The association of metabolic unhealthiness with stroke appeared more clearly in
 8 analysis stratified by BMI groups (**Table 3**). In both non-obese and obese individuals,
 9 the metabolically unhealthy were at increased risk of ischemic stroke compared to
 10 the metabolically healthy (for non-obese: HR 1.68, 95%CI 1.52-1.87; for obese: HR
 11 2.16, 95% CI 1.79-2.60). The association seemed to become stronger with increasing
 12 degree of obesity.

13
 14 **Table 3. The association of metabolic health status with ischemic stroke**
 15 **stratified by body mass index groups**

	N	Stroke cases	HR (95% CI)
Non-obese (BMI 18.5-24.9 kg/m²)			
Metabolically healthy	110,531	465 (0.4%)	1 (reference)
Metabolically unhealthy	130,583	2,535 (1.9%)	1.68 (1.52-1.87)
Obese (BMI ≥ 25 kg/m²)			
Metabolically healthy	26,448	121 (0.5%)	1 (reference)
Metabolically unhealthy	86,521	1,763 (2.0%)	2.16 (1.79-2.60)
Normal weight (BMI 18.5-22.9 kg/m²)			
Metabolically healthy	79,084	306 (0.4%)	1 (reference)
Metabolically unhealthy	73,017	1,409 (1.9%)	1.71 (1.51-1.95)
Overweight (BMI 23.0-24.9 kg/m²)			
Metabolically healthy	31,447	159 (0.5%)	1 (reference)
Metabolically unhealthy	57,566	1,126 (2.0%)	1.58 (1.33-1.87)

Stage I obesity (BMI 25-29.9 kg/m ²)			
Metabolically healthy	24,861	115 (0.5%)	1 (reference)
Metabolically unhealthy	76,796	1,585 (2.1%)	2.13 (1.76-2.59)
Stage II obesity (BMI ≥ 30 kg/m ²)			
Metabolically healthy	1,587	6 (0.4%)	1 (reference)
Metabolically unhealthy	9,725	178 (1.8%)	2.32 (1.02-5.29)

HR = Hazard ratio; CI = Confidence interval; BMI = body mass index

Adjusted for age, sex, income, area, smoking, drinking, exercise, history of ischemic heart disease, peripheral artery disease, congestive heart failure, transient ischemic attack, venous thromboembolism, chronic obstructive pulmonary disease, end-stage renal disease, liver cirrhosis, cancer, and cardiac surgery

Meanwhile, the association of obesity with ischemic stroke differed according to metabolic health status (**Table 4**). In metabolically healthy individuals, increased BMI did not increase the risk for ischemic stroke (HR 1.00, 95%CI 0.81-1.22), regardless of the severity of obesity. Meanwhile, in metabolically unhealthy individuals, being obese was significantly associated with increased risk of stroke (HR 1.19, 95%CI 1.12-1.27), and this association became stronger with increasing BMI.

Table 4. The association of body mass index with ischemic stroke stratified by metabolic health status

	N	Stroke cases	HR (95% CI)
Metabolically healthy			
Non-obese (BMI 18.5-24.9 kg/m ²)	110,531	465 (0.4%)	1 (reference)
Obese (BMI ≥ 25 kg/m ²)	26,448	121 (0.5%)	1.00 (0.81-1.22)
BMI 18.5-22.9 kg/m ² (Normal weight)	79,084	306 (0.4%)	1 (reference)
BMI 23.0-24.9 kg/m ² (Overweight)	31,447	159 (0.5%)	1.15 (0.95-1.39)

BMI 25-29.9 kg/m ² (Stage I obesity)	24,861	115 (0.5%)	1.04 (0.84-1.29)
BMI ≥ 30 kg/m ² (Stage II obesity)	1,587	6 (0.4%)	1.11 (0.49-2.49)
Metabolically unhealthy			
Non-obese (BMI 18.5-24.9 kg/m ²)	130,583	2,535 (1.9%)	1 (reference)
Obese (BMI ≥ 25 kg/m ²)	86,521	1,763 (2.0%)	1.19 (1.12-1.27)
BMI 18.5-22.9 kg/m ² (Normal weight)	73,017	1,409 (1.9%)	1 (reference)
BMI 23.0-24.9 kg/m ² (Overweight)	57,566	1,126 (2.0%)	1.11 (1.02-1.20)
BMI 25-29.9 kg/m ² (Stage I obesity)	76,796	1,585 (2.1%)	1.24 (1.15-1.33)
BMI ≥ 30 kg/m ² (Stage II obesity)	9,725	178 (1.8%)	1.31 (1.12-1.54)

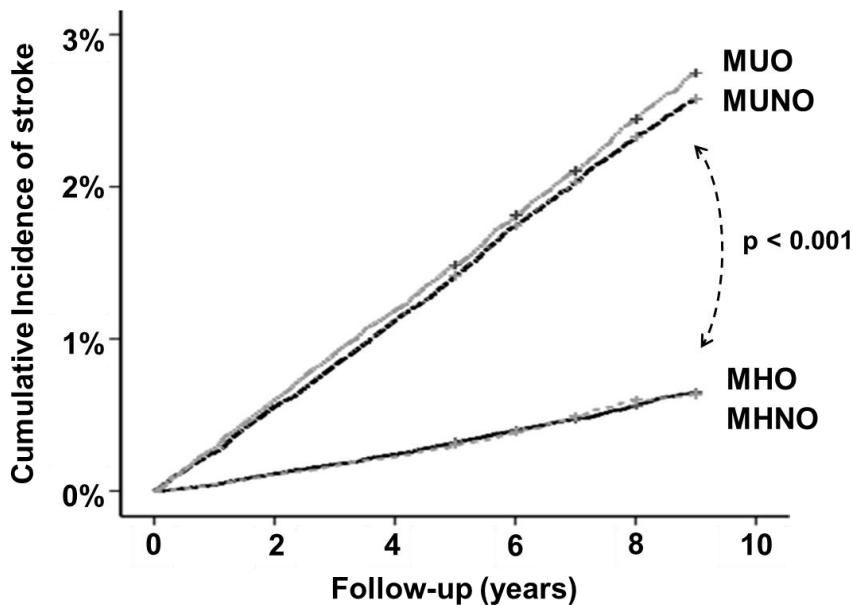
1 HR = Hazard ratio; CI = Confidence interval; BMI = body mass index
2 Adjusted for age, sex, income, area, smoking, drinking, exercise, history of ischemic heart disease,
3 peripheral artery disease, congestive heart failure, transient ischemic attack, venous thromboembolism,
4 chronic obstructive pulmonary disease, end-stage renal disease, liver cirrhosis, cancer, and cardiac
5 surgery
6

7 **Incidence and risk of stroke according to obesity and** 8 **metabolic healthiness**

9 During mean follow-up of 7.43 years, (SD, 1.52 years), total 4,884 (1.4%) cases of
10 newly diagnosed ischemic stroke were detected (incidence rate, 1.86 per 1,000
11 person-years). The cumulative incidence of ischemic stroke for each group are
12 shown in Kaplan-Meier curves (**Figure 4**). Stroke incidence was significantly
13 increased in the metabolically unhealthy groups (MUNO, MUO) compared to the
14 metabolically healthy groups (MHNO, MHO) ($p < 0.001$ by log rank test), while
15 there was no significant difference between the MHNO and MHO groups ($p = 0.409$)
16 or between the MUNO and MUO groups ($p = 0.064$). Stroke incidence rates were
17 nearly same in metabolically healthy MHNO and MHO groups (0.56 and 0.61 per
18 1,000 person-years), while they were more than four-fold higher in metabolically
19 unhealthy MUNO and MUO groups (2.61 and 2.76 per 1,000 person-years) (**Table**

1 5). Risk for ischemic stroke was not increased in MHO compared to MHNO
 2 individuals, both before and after multivariate adjustment (adjusted HR 0.99, 95%CI
 3 0.81-1.20), and in both younger and older ages. Meanwhile, stroke risk was
 4 significantly increased in both metabolically unhealthy groups (MUNO and MUO)
 5 compared to MHNO individuals.
 6

Figure 4



Number of Patients at Risk

MHNO	110,531	110,428	101,831	76,800	30,162
MUNO	130,583	129,943	120,241	91,543	36,107
MHO	26,448	26,424	24,350	18,406	7,259
MUO	86,521	86,059	79,316	59,405	22,996

7

8 **Figure 4. Kaplan-Meier curves showing the incidence of ischemic stroke**
 9 **according to groups categorized by obesity and metabolic health.**

10 P-value for comparison by log-rank test.

11

1 **Table 5. Incidence and risk of ischemic stroke according to groups divided by**
 2 **obesity and metabolic health**

	MHNO (n=110,531)	MUNO (n=130,583)	MHO (n=26,448)	MUO (n=86,521)
Stroke cases, n (%)	465 (0.4%)	2,535 (1.9%)	121 (0.5%)	1,763 (2.0%)
Stroke incidence (per 1,000 person- years)	0.56	2.61	0.61	2.76
Hazard ratio (HR)				
Crude [†] HR (95% CI)	1 (ref)	4.62 (4.19-5.10)	1.09 (0.89-1.33)	4.90 (4.42-5.42)
Adjusted [‡] HR (95% CI)	1 (ref)	1.72 (1.55-1.90)	0.99 (0.81-1.20)	2.06 (1.85-2.28)
Age < 50	1 (ref)	1.57 (1.25-1.95)	1.01 (0.70-1.46)	2.38 (1.90-2.97)
Age ≥ 50	1 (ref)	1.64 (1.46-1.84)	0.94 (0.74-1.20)	1.87 (1.66-2.10)

3 † Unadjusted crude hazard ratio (HR) and 95% confidence interval (CI); ‡ Adjusted for age, sex,
 4 income, area, smoking, drinking, exercise, history of ischemic heart disease, peripheral artery disease,
 5 congestive heart failure, transient ischemic attack, venous thromboembolism, chronic obstructive
 6 pulmonary disease, end-stage renal disease, liver cirrhosis, cancer, and cardiac surgery

7

8 The same was valid for groups further divided by BMI and metabolic health status
 9 (**Table 6**): MHNW (metabolically healthy normal weight), MHOW (metabolically
 10 healthy overweight), MHO1 (metabolically healthy obesity stage I), MHO2
 11 (metabolically healthy obesity stage II), MUNW (metabolically unhealthy normal
 12 weight), MUOW (metabolically unhealthy overweight), MUO1 (metabolically
 13 unhealthy obesity stage I), and MUO2 (metabolically unhealthy obesity stage II).
 14 Stroke incidence was significantly increased in the metabolically unhealthy groups,

1 while there was no significant difference between the metabolically healthy groups.
 2 In the metabolically unhealthy groups, stroke risk seemed to increase the higher the
 3 BMI interval (**Figure 5**).

4

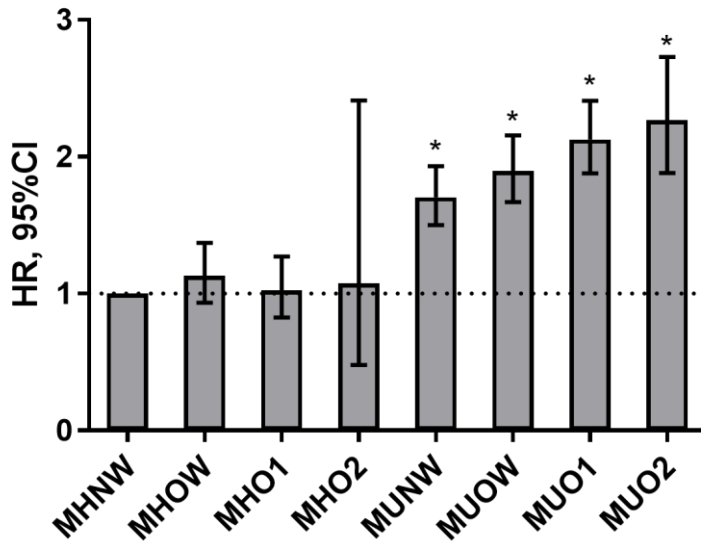
5 **Table 6. Incidence and risk of ischemic stroke according to groups further**
 6 **divided by body mass index and metabolic health**

	MHNW (n=79,084)	MHOW (n=31,447)	MHO1 (n=24,861)	MHO2 (n=1,587)
Stroke cases, n (%)	306 (0.4%)	159 (0.5%)	115 (0.5%)	6 (0.4%)
Stroke incidence (per 1,000 person-years)	0.52	0.68	0.62	0.52
Hazard ratio (HR)				
Crude [†] HR (95% CI)	1 (ref)	1.30 (1.07- 1.58)	1.19 (0.96- 1.48)	1.01 (0.45- 5.65)
Adjusted [‡] HR (95% CI)	1 (ref)	1.13 (0.93- 1.37)	1.03 (0.83- 1.27)	1.07 (0.48- 2.41)
	MUNW (n=73,017)	MUOW (n=57,566)	MUO1 (n=76,796)	MUO2 (n=9,725)
Stroke cases, n (%)	1,409 (1.9%)	1,126 (2.0%)	1,585 (2.1%)	178 (1.8%)
Stroke incidence (per 1,000 person-years)	2.60	2.62	2.79	2.54
Hazard ratio (HR)				
Crude [†] HR (95% CI)	5.00 (4.42- 5.65)	5.05 (4.45- 5.73)	5.37 (4.75- 6.07)	4.90 (4.07- 5.89)
Adjusted [‡] HR (95% CI)	1.70 (1.50- 1.93)	1.90 (1.67- 2.16)	2.13 (1.88- 2.41)	2.27 (1.88- 2.73)

7 [†] Unadjusted crude hazard ratio (HR) and 95% confidence interval (CI); [‡] Adjusted for age, sex, income,
 8 area, smoking, drinking, exercise, history of ischemic heart disease, peripheral artery disease,

1 congestive heart failure, transient ischemic attack, venous thromboembolism, chronic obstructive
2 pulmonary disease, end-stage renal disease, liver cirrhosis, cancer, and cardiac surgery
3

Figure 5



4
5 **Figure 5. Risk for ischemic stroke according to groups divided by BMI and**
6 **metabolic health.**

7 Bars representing hazard ratios (HRs) with error bars for 95% confidence intervals (95% CI). Asterisks
8 indicated significant difference with reference group.

9

10

11 **Discussion**

12 **Stroke risk associated with obesity differs according to** 13 **metabolic health status**

14 The main finding of this study was that MHO individuals did not show increased
15 risk for ischemic stroke compared to healthy non-obese individuals, while

1 metabolically unhealthy individuals, both non-obese and obese, showed increased
2 risk for stroke. While obesity appears to be significantly associated with ischemic
3 stroke, this effect may differ according to metabolic health status: being obese
4 increased risk for stroke in metabolically unhealthy individuals, but not in
5 metabolically healthy individuals. Meanwhile, all metabolic health components
6 showed stronger association with stroke than obesity, and being metabolically
7 unhealthy increased risk for stroke in all BMI categories.

8 Obesity is associated with an increased risk for stroke. We used BMI as a measure
9 of obesity, which is easily obtained and routinely measured in large population
10 studies, and while it is moderately strongly correlated (30–50%) with fat-free mass,
11 it is much more strongly correlated (60–90%) with fat mass and also (80–85%) with
12 waist circumference[19]. Obesity was associated with 40% increased stroke
13 mortality with each 5-kg/m² increase in the BMI range of 25-50 kg/m²[19]; in a
14 meta-analysis, the relative risk for ischemic stroke was 1.22 (95% CI, 1.05–1.41) for
15 overweight and 1.64 (95% CI, 1.36–1.99) for obesity[20]. However, there is
16 conflicting data on whether obese individuals without metabolic syndrome risk
17 factors also have increased risk for stroke. One study of 5,171 subjects with 9.1 years
18 of follow-up found that MHO did not show greater risk for ischemic stroke compared
19 to metabolically healthy non-obese subjects (HR 1.07, 95% CI 0.93-1.24)[6], even
20 though MHO was defined as having up to 1 risk factors. Another study that followed
21 19,675 participants for 18.7 years, found that MHO (having 0 risk factors) did not
22 have increased risk for not only stroke, but coronary heart disease and overall
23 mortality as well, and only showed moderate increase in risk for diabetes[7]. Other
24 studies that included stroke as part of cardiovascular outcome found that MHO did
25 not show difference in risk compared to the metabolically healthy non-obese [8, 9].
26 On the other hand, the Whitehall II study followed up 7,122 subjects for 17.4 years,

1 and found that MHO subjects were at increased risk for cardiovascular disease
2 including stroke (HR 1.95, 95%CI 1.37-2.77), and that stroke analyzed separately
3 showed similar results[3]. However, this study defined MHO as having 0-1 risk
4 factor, and stroke included cerebral hemorrhage as well as ischemic stroke. Some
5 other studies including stroke in cardiovascular outcome also found that risk was
6 increased in MHO compared to MHNO[4, 5].

7

8 **MHO and cardiovascular risk under debate**

9 The existence of a MHO phenotype with lower cardiovascular risk remains under
10 debate. The inconsistent evidence may be related to several factors. First, the
11 definition of metabolic health is extremely important and different definitions may
12 lead to different results. Metabolic syndrome is defined as having 3 or more of 5 risk
13 factors, and so many have considered metabolically healthy to be its opposite, i.e.
14 having 1 or less of 4 risk factors (excluding waist circumference). However, it has
15 been argued that a person with even 1 risk factor, such as impaired glucose tolerance
16 or treatment for hypertension, cannot be considered truly metabolically healthy[16].
17 Many previous studies defined MHO as obese persons with up to 1 metabolic risk
18 factor, and including these people may have confounded results by increasing
19 cardiovascular risk for the thus defined MHO group. According to a recently
20 proposed harmonized definition of MHO[16], a person should have none of the
21 metabolic syndrome risk factors to be considered metabolic healthy. We adopted this
22 stricter definition restricting MHO to those who are obese but fully healthy from a
23 metabolic point of view. In a previous study, when defining MHO as being obese
24 and having 0 risk factors, the prevalence of MHO among the obese was 16.6%, while
25 it increased nearly double-fold to 31.7% when those having up to 1 risk factor were
26 included[21]. In another large study defining MHO as meeting 0 metabolic

1 syndrome criteria, the prevalence of MHO was 7-28% in women, and 2-19% in
2 men[22]. In our cohort, a third (31.9%) were obese, of whom a fourth (23.4%) were
3 metabolically healthy; thus, 7.5% of the population were MHO.
4 Second, the prognosis of MHO may be outcome specific; for example,
5 cardiovascular disease and type 2 diabetes showed different associations[3, 8].
6 Coronary heart disease and ischemic stroke are often studied as a composite
7 cardiovascular outcome, but may have different associations with obesity and
8 metabolic health components, leading to inexact results. In some previous studies
9 where MHO showed increased cardiovascular risk, the relative risk for stroke was
10 less than that for coronary heart disease[7]. We recently reported that MHO
11 individuals are at increased risk of atrial fibrillation (AF), and obesity is
12 independently associated with AF development[10]. Despite the increased risk of AF,
13 in this study, we found that MHO individuals did not show an increased risk of stroke
14 compared to healthy non-obese individuals. Stroke risk may also differ depending
15 on type of stroke, i.e. ischemic or hemorrhagic[23-25]; however, most studies on
16 MHO did not differentiate types of stroke in the outcome[3-5, 7, 9]. Focusing on a
17 single outcome would be ideal, if the study population was large enough. In this
18 study, we confined the primary outcome to ischemic stroke in a population
19 sufficiently large to obtain meaningful results.

20

21 **Study strengths and limitations**

22 Several notable strengths of our study include its large sample size of over 354,000
23 adults, representability of the general Korean population, and assessment of
24 outcomes over a more than 7-year follow-up period. All records of medical treatment
25 were available for each individual in the cohort, leading to greater accuracy in
26 detection of the primary outcome. In addition, a strict definition of MHO was used,

1 making it possible to follow the prognosis of the obese who are fully metabolically
2 healthy. Also, we focused on a single outcome instead of a composite cardiovascular
3 outcome.

4 Our study also has some limitations. First, comorbidities were identified by diagnosis
5 codes included in claims data, with a minimum requirement of number of outpatient
6 or inpatient treatments. This relies on the assumption that the physician entered the
7 correct diagnosis for each patient. Second, only total cholesterol levels were
8 available and we used this as substitute for triglyceride and HDL levels in metabolic
9 health criteria. Third, as the study cohort was followed up for a mean period of 7-8
10 years, it would be unable to detect an increase in the primary outcome if it happened
11 after a lag of 10-15 years. However, in the above-mentioned Whitehall study,
12 Kaplan-Meier survival curves for outcome diverged from the start of the study, not
13 after a lag time[3]. Also in our previous study, 25% of the MHO group and 15% of
14 the MHNO group were shown to become metabolically unhealthy after 7.5 years of
15 follow-up, and these subgroups showed increased risk for AF[10]. Thus, a longer
16 follow-up period may lead to a higher portion of initially metabolically healthy
17 groups becoming metabolically unhealthy and thereby showing an increase in
18 outcome. Fourth, as the cohort was homogeneously comprised of Koreans, there may
19 be limitations in generalizing our findings to other ethnicities.

20

21 **Conclusion**

22 In conclusion, obesity increased risk for ischemic stroke in the metabolic unhealthy,
23 while not in the metabolically healthy. Obesity appears to be harmful especially in
24 persons with metabolic risk factors, and maintaining normal weight may be more
25 important for this population. On the other hand, MHO individuals were not at
26 increased risk for ischemic stroke, and metabolically healthy obesity may be benign,

1 at least in the case of ischemic stroke. Better understanding of the health risks
2 associated with obesity can help physicians discern patients who should engage in
3 weight reduction more actively. Also, metabolic unhealthiness showed greater
4 association than obesity with stroke, stressing the importance of controlling
5 metabolic risk factors.

6

7

8

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- 14
15

1 Supplements

2 Supplementary Table 1. International Classification of Disease (ICD) 10 codes 3 and procedure codes used for variables

Variables	ICD-10 codes	Procedure codes	Requisites
Hypertension	I10-15		*
Diabetes mellitus	E11-14		† and prescription of hypoglycemic drugs
Dyslipidemia	E78		†
Ischemic heart disease	I20-25		*
Peripheral artery disease	I70, I73		*
Congestive heart failure	I50		†, in the previous 3 years
Transient ischemic attack	G458, G459		†
Venous thromboembolism	I26, I80		≥ 1 diagnosis during hospitalization, in the previous 1 year
End-stage renal disease	N18, N19, Z49, Z905, Z94, Z992	R3280 (kidney transplantation), O7011-7020 (hemodialysis), O7017, O7075 (peritoneal dialysis)	≥ 1 diagnosis during hospitalization or at outpatient clinic and ≥ 1

			procedure code, in the previous 3 years ≥ 1 diagnosis during hospitalization , in the previous 1 year
Liver cirrhosis	K703, K743- 745, K76		
Chronic obstructive pulmonary disease	J43-44		†
Cancer	C00-97		*
		O1660, O1671-1672, O1680, O1690, O1701-1705, O1710-1711, O1721-1723, O1730, O1740, O1750, O1760, O1770, O178-1783, O1791-O1798, O1800, O1810, O1821-1826, O1830, O1840-1844, O1850, O1861, O1873-1875, O1878-1879, O1890, O1895, O1901-1902, O1910, O1921-1922, O1931-1932, O1935, O1940, O1950, O1960, O1970, O1981- 1982, O2001-2002, O2004-2007	†

1 * ≥ 1 diagnosis during hospitalization, or ≥ 2 diagnoses at outpatient clinic, in the previous 1 year

2 † ≥ 1 diagnosis during hospitalization or at outpatient clinic, in the previous 1 year

3

4

5

1 요약 (국문초록)

2

3 서론

4 비만은 뇌경색 증가의 위험요인으로 알려져 있지만, 대사적으로 건강한
5 비만도 뇌경색의 위험이 증가하는지에 대해서는 논란이 있다. 이
6 논문에서는 대사적으로 건강한 비만에서 뇌경색의 위험이 증가하는지를
7 중점으로 하여 비만과 대사증후군 요소들이 뇌경색에 미치는 영향을
8 연구하였다.

9 방법

10 국민건강보험공단 표본 코호트에서 2002-2008 년도에 등록된
11 354,083 명의 성인들을 추출하여 뇌경색 발생 여부를 2013 년도까지
12 추적관찰 하였다. 비만은 체질량지수 (body mass index, BMI) \geq 25
13 kg/m² 으로 정의하였다. 대사증후군 기준요소들이 없는 대상자들은
14 ‘대사적으로 건강하다’, 위험요소 하나 이상 있는 대상자들은
15 ‘대사적으로 건강하지 못하다’ 고 정의하였다. 코호트는 비만과
16 대사적으로 건강한지 여부에 따라 다음과 같이 4 가지 군으로
17 분류하였다: 대사적으로 건강한 정상체중 (metabolically healthy non-obese,
18 MHNO), 대사적으로 건강하지 못한 정상체중 (metabolically unhealthy non-
19 obese, MUNO), 대사적으로 건강한 비만 (metabolically healthy obese, MHO),
20 대사적으로 건강하지 못한 비만 (metabolically unhealthy obese, MUO).

21 결과

22 평균 7.4 \pm 1.5 년 추적관찰 한 결과 4,884 명(1.4%)에서 뇌경색이
23 새로 발생하였다. BMI 가 높을수록 뇌경색 위험이 유의하게 증가하는

1 것으로 나타났으나, 대사적으로 건강한지 여부에 따라서 BMI 의 영향이
2 달라졌다. 대사적으로 건강한 대상자들에서는 비만의 여부나 비만의
3 정도가 뇌경색 위험을 증가시키지 않았다. 반면, 대사적으로 건강하지
4 못한 대상자들에서는 비만이 유의하게 뇌경색 위험을 증가시켰다.
5 뇌경색 발생율은 MHNO, MUNO, MHO, MUO 군에서 1,000 인년(person-
6 years)당 각각 0.56, 2.61, 0.61, 2.76 이었다. 다변량회귀분석을 하였을
7 때 대사적으로 건강하지 못한 군에서는 뇌경색 위험이 유의하게
8 증가하였지만, 대사적으로 건강한 비만에서는 대사적으로 건강한
9 정상체중 군에 비해 뇌경색 위험도의 차이가 없었다.

10 결론

11 대사적으로 건강한 비만에서 뇌경색 위험은 증가하지 않았다. 하지만
12 대사적 위험요소가 있는 사람들에서는 비만이 뇌경색의 위험을
13 증가시켰고, 이러한 사람들에게는 정상체중을 유지하는 것이 더 중요할
14 수 있다. 대사적 위험요소가 있는 것이 비만보다 뇌경색과 더 큰 연관을
15 보였다.

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18 주요어: 비만, 대사증후군, 대사적으로 건강한 비만, 뇌경색, 역학,
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