

Different Effects of Metabolic Syndrome on Dementia According to Dementia Type: Analysis Based on the National Health Insurance Service Database of Gangwon Province in South Korea

YEO JIN KIM

Chuncheon Sacred Heart Hospital

Sang Mi Kim

Ewha Womans University

Dae Hyun Jeong

Research Institute for Gangwon

Sang-Kyu Lee

Chuncheon Sacred Heart Hospital

Moo-Eob Ahn

Chuncheon Sacred Heart Hospital

Ohk-Hyun Ryu (✉ ohryu30@gmail.com)

<https://orcid.org/0000-0003-1118-6886>

Research

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Abstract

Background

Metabolic syndrome is a cluster of conditions that occur together, increasing the risk of cardiovascular disease. However, the relationship between metabolic syndrome and dementia has remained controversial. Using nationwide population cohort data, we investigated the association between metabolic syndrome and dementia, according to the dementia type.

Methods

We analyzed data of 84,144 individuals, in the aged group of more than 60 years, between January 1, 2009, to December 31, 2009, at Gangwon province by using the information of the (Korean) National Health Insurance Service. After eight years of gap, in 2017, we investigated the relationship between metabolic syndrome and dementia. We classified Dementia either as dementia of the Alzheimer type (AD) or vascular dementia (VD). AD and VD were defined according to criteria in the International Classification of Disease, Tenth Revision, Clinical Modification codes.

Results

Metabolic syndrome was associated with AD, while it was not associated with VD. All five components of metabolic syndrome were associated with AD, independently. However, among components of metabolic syndrome, only the high glucose level was associated with VD. Body Mass Index (BMI), fasting glucose and smoking were also associated with AD. A history of the previous stroke was associated with both AD and VD.

Conclusions

Metabolic syndrome was associated with AD, while was not associated with VD. VD was associated only with several risk factors that could affect the vascular state rather than a metabolic syndrome. We suggested that the effect of metabolic syndrome on dementia would be different depending on the type of dementia.

Background

Metabolic syndrome is a cluster of components that indicates overnutrition and includes five components that are high blood pressure (BP), high blood glucose, high serum triglycerides (TG), low serum high-density lipoprotein cholesterol (HDL-C) and abdominal obesity. In particular, high blood pressure and blood glucose are the components of metabolic syndrome that are well known to be associated with dementia in late life. [1, 2] Metabolic syndrome has a greater potential to result in type 2 diabetes, lipid disorders, cardiovascular disease, stroke, and other circulatory disorders. Among them, cardiovascular and related diseases are the highest risk factor associated with metabolic syndrome, but whether cardiovascular diseases have any connection with dementia is not known. Previous studies between metabolic syndrome and cognitive impairment were inconsistent. Some studies reported that metabolic syndrome was associated with increased risk of cognitive impairment, [3, 4] while other studies reported no association between the two, [5, 6] and even some reported that metabolic syndrome decelerated cognitive impairment. [7]

Of the numerous dementia etiologies, Alzheimer's disease (AD) is the most common type of dementia, about 60% of the cases. Vascular dementia (VD) is the second most common type, accounting for about 20% of dementia. Cardiovascular risk factors could affect the development of both types, but the extent of their influences would depend on the type of dementia. VD had a leading cause in most cases, such as ischemia, haemorrhage, anoxia, or hypoxia, while causes of Alzheimer's disease are not well understood. [8] Yet, previous studies that investigated the relationship between dementia and metabolic syndrome usually did not consider the type of dementia.

Gangwon province is located in the northeastern part of South Korea and is divided into two areas by the Mountains. It has an aged society with a relatively low population density in Korea. Although a large part of the population resides in the urban area, 11 out of 18 administrative areas have inadequate medical facilities because of the presence of mountains. That means this area is one of the most vulnerable areas of medical service in South Korea. The risk factors related to metabolic syndrome (cardiovascular and related diseases) are not well managed in this region therefore, characteristics of the disease might be different from other regions. Therefore, we analyzed the association of metabolic syndrome and its five components with the incident of dementia (a gap of eight years), according to the dementia type, in a population-based sample in Gangwon province, South Korea.

Methods

Data source and study population

The present study was conducted using data from the South Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC), which includes demographic information, medical use, disease information, lifestyle habits, and basic laboratory data. [9, 10] The NHIS registration is mandatory for all Koreans and the NHIS database represents health information for almost all populations in Korea. [11]

Patient data of Gangwon province in South Korea from January 1, 2009, to December 31, 2009, was included (n = 455,859). Of these patients, we selected only those aged more than 60 years (n = 105,786). Patients with dementia who was diagnosed before the index day were excluded (n =

21,642). In the end, 84,144 individuals were included in this study. We defined diagnoses using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board of Chuncheon Sacred Heart Hospital, and all methods were performed in accordance with the approved guidelines and regulations.

Definition of dementia

For defining dementia of the Alzheimer type (AD), the code of F00 or G30 was included but F01, F02, F03, F051, and G31 were excluded. For the definition of vascular dementia (VD), codes of F02 were included.

Definition of Metabolic syndrome

Individuals who met three or more of the five components were defined as having metabolic syndrome. Five components were abdominal obesity, high TG level, reduced HDL-C level, elevated BP, and elevated blood glucose.[12] Individuals having abdominal obesity were defined if waist circumference were over 90 cm in males and 80 cm in the female. Individuals having high TG level were defined if the serum TG level was over 150 mg/dL. Individuals having low HDL-C level were defined if serum HDL-C level was lower than 40 mg/dL in male and 50 mg/dL in the female. Individuals were defined as having elevated blood pressure if anti-hypertensive medications were prescribed or systolic blood pressure more than 130 mmHg and/or diastolic blood pressure more than 85 mmHg was recorded. Individuals having high blood glucose were defined if anti-diabetic drugs (insulins, sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and α -glucosidase inhibitors) were prescribed or fasting serum glucose level was over 100 mg/dL.

Statistical analysis

The baseline characteristics based on the data from the NHIS database are presented as mean values \pm standard deviation (SD) for continuous variables and percentages for categorical variables. Differences between the metabolic syndrome group and non-metabolic syndrome group were confirmed using the Student t-test for continuous variables and chi-square tests for categorical variables. The relationship of metabolic syndrome and each component of metabolic syndrome for dementia was evaluated using multiple logistic regression analysis. We ran three regression models. In model 1, we performed multiple logistic regression analysis with metabolic syndrome or each of the components as determinant and AD or VD as outcome variables after controlling for age and gender. In model 2, we performed multiple logistic regression analysis with age, gender, smoking, alcohol, physical inactivity, and metabolic syndrome or five metabolic syndrome components (high TG, high BP, high blood glucose, abdominal obesity, and low HDL-C). In model 3, we performed multiple logistic regression analysis with age, gender, smoking, alcohol, physical inactivity, previous stroke, previous cardiac disease and metabolic syndrome or five metabolic syndrome components (high TG, high BP, high glucose, abdominal obesity, and low HDL-C). Again, the relationship of other vascular risk factors for dementia was evaluated using multiple logistic regression analysis. We also ran three regression models in this analysis. In model 1, we performed multiple logistic regression analysis with vascular risk factors as determinant and AD or VD as outcome variables after controlling for age and gender. In model 2, we performed multiple logistic regression analysis with age, gender, smoking, metabolic syndrome, BMI, systolic BP, diastolic BP, fasting glucose, total cholesterol. In model 3, we performed multiple logistic regression analysis with age, gender, smoking, metabolic syndrome, BMI, systolic BP, diastolic BP, fasting glucose, total cholesterol, smoking, alcohol, physical inactivity, previous stroke, and previous cardiac disease. Disease risks were expressed as the odds ratio (OR) with 95% confidence interval (95% CI). We defined statistical significance as $p < 0.05$. Statistical analyses were conducted with SPSS version 25 software (SPSS Inc., Chicago, IL, USA).

Data availability

The original anonymized data used in this analysis was obtained from the NHIS of South Korea. The dataset from NHIS is not publicly available due to restricted access. However, any researcher requiring access to the data can obtain it directly through a license agreement, including the payment of appropriate license fees.

Results

Demographics and baseline characteristics

Detailed demographic and clinical characteristics of the participants are presented in Table 1. 40.2% of participants had metabolic syndrome. The mean age of the metabolic syndrome group was higher than the non-metabolic syndrome group. The metabolic syndrome group had a higher proportion of females than the non-metabolic syndrome group. The non-metabolic syndrome group had a higher level of physical inactivity, however, they also more engaged in smoking and alcohol intake. The mortality rate of both groups was similar.

After eight years, of the 33,828 patients with metabolic syndrome, 1,380 patients converted to AD and 335 patients converted to VD. Of the 50,316 patients with the non-metabolic syndrome, 176 patients converted to AD and 380 patients converted to VD.

Table 1
Demographics and baseline characteristics

	Metabolic syndrome (n = 33,828)	Non-metabolic syndrome (n = 50,316)	p value
Mean age	67.42 ± 5.28	66.79 ± 5.11	< 0.0001
Gender, female number ^a	23,020 (68.1)	25,088 (49.9)	< 0.0001
BMI	25.88 ± 2.96	23.68 ± 2.90	< 0.0001
Systolic BP	136.61 ± 15.15	126.54 ± 15.91	< 0.0001
Diastolic BP	82.03 ± 10.12	77.18 ± 9.97	< 0.0001
Fasting glucose	112.14 ± 31.27	96.70 ± 20.45	0.001
Total cholesterol	200.80 ± 46.30	194.55 ± 38.46	< 0.0001
Smoking, pack-year	1.33 ± 4.89	2.16 ± 5.99	< 0.0001
Alcohol, cup/week	1.20 ± 2.94	1.54 ± 3.20	< 0.0001
Previous stroke ^a	804(2.38)	876(1.74)	< 0.0001
Previous cardiac disease ^a	2,137(62.2)	2,513(5.8)	< 0.0001
Previous HTN ^a	18,062(62.2)	17,180(39.6)	< 0.0001
Previous DM ^a	6,969(24.1)	4,102(9.5)	< 0.0001
Previous dyslipidemia ^a	2,225(7.7)	2,493(5.8)	< 0.0001
Physical inactivity ^a	5,487(29.8)	9,483(35.0)	< 0.0001
High TG ^a	21,746 (64.3)	7,617 (15.1)	< 0.0001
High BP ^a	27,571 (81.5)	22,848 (45.4)	< 0.0001
High glucose ^a	22,422 (33.7)	12,804 (74.6)	< 0.0001
Abdominal obesity ^a	26,806 (79.2)	14,939 (29.7)	< 0.0001
Low HDL-C ^a	19,768 (58.4)	8,377 (16.65)	< 0.0001
Data are mean ± SD unless otherwise indicated			
a Number (%)			
Abbreviations: BMI, body mass index; SD, standard deviation; BP, blood pressure; HTN, hypertension; DM, diabetes mellitus; TG, triglyceride; HDL-C, high density lipoprotein cholesterol			

Association between metabolic syndrome and AD

Table 2 shows the risk of AD according to the metabolic syndrome and component of the definition of metabolic syndrome.

Metabolic syndrome was associated with AD. (OR 11.476, 95% CI 9.026, 14.591, $p < 0.0001$). All five components of metabolic syndrome were also associated with AD independently. Patients with high TG had 1.872-fold odds of AD (OR 1.872, 95% CI 1.604, 2.185, $p < 0.001$). Patients with high BP had 1.847-fold odds of AD (OR 1.847, 95% CI 1.545, 2.209, $p < 0.0001$). Patients with high glucose levels had 1.767-fold odds of AD (OR 1.767, 95% CI 1.516, 2.058, $p < 0.0001$). Patients with obesity had 1.879-fold odds of Alzheimer's disease (OR 1.879, 95% CI 1.567, 2.253, $p < 0.0001$). Patients with low HDL-C had 1.913-fold odds of AD (OR 1.913, 95% CI 1.633, 2.241, $p < 0.0001$).

Table 2
Metabolic syndrome and odds of the dementia in Alzheimer's type

	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
MetS	10.577 (9.018,12.406)	< 0.0001	12.028 (9.579,15.102)	< 0.0001	11.476 (9.026,14.591)	< 0.0001
High TG	2.264 (2.38,2.924)	< 0.0001	2.003 (1.734,2.314)	< 0.0001	1.872 (1.604,2.185)	< 0.0001
High BP	1.873 (1.665,2.108)	< 0.0001	1.783 (1.514,2.100)	< 0.0001	1.847 (1.545,2.209)	< 0.0001
High glucose	2.308 (2.308,2.08)	< 0.0001	1.838 (1.595,2.118)	< 0.0001	1.767 (1.516,2.058)	< 0.0001
Abdominal obesity	2.368 (2.099,2.671)	< 0.0001	1.773 (1.501,2.093)	< 0.0001	1.879 (1.567,2.253)	< 0.0001
Low HDL-C	2.332 (2.098,2.592)	< 0.0001	1.952 (1.685,2.262)	< 0.0001	1.913 (1.633,2.241)	< 0.0001
Model 1: separate models associated each exposure variable with Alzheimer's disease with adjustment for age and gender						
Model 2: single model including age, gender, smoking, alcohol, physical inactivity and metabolic syndrome or 5 metabolic syndrome components (high TG, high BP, high glucose, abdominal obesity, low HDL-C)						
Model 3: single model including age, gender, smoking, alcohol, physical inactivity, previous stroke, previous cardiac disease and metabolic syndrome or 5 metabolic syndrome components (high TG, high BP, high glucose, abdominal obesity, low HDL-C)						
Abbreviations: OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure						

Association between metabolic syndrome and VD

Table 3 shows the risk of VD according to the metabolic syndrome and component of the definition of metabolic syndrome.

Metabolic syndrome was not associated with VD (OR 1.173, 95% CI 0.940, 1.465, $p = 0.158$) Among five components of metabolic syndrome, high glucose was associated with VD independently. Patients with high glucose had 1.255-fold odds of VD (OR 1.255, 95% CI 1.008, 1.561, $p = 0.042$). High TG, high BP, obesity and low HDL-C were not associated with VD.

Table 3
Metabolic syndrome and odds of vascular dementia

	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
MetS	1.084 (1.023, 1.148)	0.006	1.171 (0.947, 1.448)	0.144	1.173 (0.940, 1.465)	0.158
High TG	1.03 (0.883, 1.202)	0.709	0.946 (0.756, 1.185)	0.631	0.902 (0.712, 1.143)	0.392
High BP	1.068 (0.915, 1.246)	0.404	1.310 (1.046, 1.642)	0.019	1.246 (0.986, 1.575)	0.066
High glucose	1.295 (1.117, 1.501)	0.001	1.286 (1.043, 1.585)	0.019	1.255 (1.008, 1.561)	0.042
Abdominal obesity	1.076 (0.919, 1.206)	0.362	0.965 (0.770, 1.209)	0.754	0.991 (0.782, 1.255)	0.939
Low HDL-C	1.028 (0.877, 1.204)	0.736	0.972 (0.772, 1.223)	0.806	0.967 (0.760, 1.230)	0.785
Model 1: separate models associated each exposure variable with Alzheimer's disease with adjustment for age and gender						
Model 2: single model including age, gender, smoking, alcohol, physical inactivity and metabolic syndrome or 5 metabolic syndrome components (high TG, high BP, high glucose, abdominal obesity, low HDL-C)						
Model 3: single model including age, gender, smoking, alcohol, physical inactivity, previous stroke, previous cardiac disease and metabolic syndrome or 5 metabolic syndrome components (high TG, high BP, high glucose, abdominal obesity, low HDL-C)						
Abbreviations: OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure						

Association between other cardiovascular risk factors included continuous metabolic parameters and dementia

BMI, fasting glucose, smoking, and previous stroke history were associated with AD (Table 4). Patients with each 1-unit kg/m² higher BMI had 0.951-fold odds of AD. (OR 0.951, 95% CI 0.927, 0.975, p < 0.0001) Patients with each 1-unit mg/dL higher fasting glucose have 1.003-fold odds of AD. (OR 1.003, 95% CI 1.001, 1.005, p = 0.003) Patients with each 1-year higher pack/year smoking had 1.020-fold odds of AD (OR 1.020, 95% CI 1.003, 1.039, p = 0.024). Patients with having previous stroke history had 1.827-fold odds of AD. (OR = 1.827, 95% CI 1.263, 2.644, p = 0.001).

Fasting glucose and previous stroke history were associated with VD. Patients with each 1-unit mg/dL higher fasting glucose had 1.004-fold odds of VD (OR = 1.004, 95% CI 1.001, 1.008, p = 0.012). Patients with having previous stroke history had 2.775-fold odds of VD. (OR = 2.775, 95% CI 1.747, 4.406, p < 0.0001).

Table 4
Odds of the dementia in Alzheimer's type or vascular dementia according to vascular risk factors

	Alzheimer's disease						Vascular dementia					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	OR (95% CI)	p value										
BMI	1.059 (1.042, 1.075)	< 0.0001	0.958 (0.941, 0.975)	< 0.0001	0.951 (0.927,0.975)	< 0.0001	1.008 (0.984, 1.032)	0.528	0.998 (0.973, 1.023)	0.857	0.988 (0.952, 1.024)	0.504
Systolic BP	1.014 (1.011, 1.017)	< 0.0001	1.000 (0.995, 1.004)	0.882	0.999 (0.992, 1.005)	0.651	1.000 (0.996, 1.005)	0.855	0.994 (0.988, 1.000)	0.063	0.999 (0.990, 1.008)	0.788
Diastolic BP	1.014 (1.009, 1.018)	< 0.0001	0.996 (0.990, 1.002)	0.214	1.001 (0.991, 1.010)	0.916	1.007 (0.999, 1.014)	0.071	1.002 (1.002, 1.022)	0.019	1.004 (0.990, 1.019)	0.575
Fasting glucose	1.009 (1.008, 1.011)	< 0.0001	1.004 (1.002, 1.005)	< 0.0001	1.003 (1.001, 1.005)	0.003	1.005 (1.003, 1.007)	< 0.0001	1.002 (1.002, 1.007)	< 0.0001	1.004 (1.001, 1.008)	0.012
Total cholesterol	1.001 (1.000, 1.002)	0.003	1.001 (1.000, 1.002)	0.211	1.000 (0.998, 1.002)	0.793	1.000 (0.999, 1.002)	0.662	0.999 (0.999, 1.002)	0.793	1.000 (0.997, 1.003)	0.998
Smoking	1.007 (0.994, 1.021)	0.282			1.020 (1.003, 1.039)	0.024	0.928 (0.892, 0.966)	< 0.0001			0.988 (0.962,1.014)	0.352
Alcohol	0.995 (0.969, 1.021)	0.694			0.979 (0.940, 1.019)	0.302	0.972 (0.936, 1.011)	0.155			1.014 (0.972,1.056)	0.525
Physical inactivity	0.935 (0.945, 1.163)	0.415			0.997 (0.838, 1.188)	0.977	0.974 (0.836, 1.136)	0.741			0.898 (0.700,1.153)	0.399
Previous stroke	2.248 (1.757, 2.874)	< 0.0001			1.827 (1.263, 2.644)	0.001	2.461 (1.753, 3.445)	< 0.0001			2.775 (1.747, 4.406)	< 0.0001
Previous cardiac disease	1.213 (1.004, 1.467)	0.046			1.088 (0.836, 1.416)	0.532	0.825 (0.598, 1.139)	0.242			0.702 (0.434, 1.136)	0.150
Model 1: separate models associated each exposure variable with Alzheimer's disease with adjustment for age and gender												
Model 2: single model including age, gender, metabolic syndrome, BMI, systolic BP, diastolic BP, Fasting glucose, total cholesterol												
Model 3: single model including age, gender, metabolic syndrome, BMI, systolic BP, diastolic BP, Fasting glucose, total cholesterol, smoking, alcohol, physical inactivity, previous stroke and previous cardiac disease												
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure												

Discussion

We investigated how metabolic syndrome and related vascular risk factors are associated with the development of dementia after eight years. Metabolic syndrome was associated with AD, while it was not associated with VD. Rather than that, high fasting glucose and previous stroke history were found associated with VD. BMI, fasting glucose, smoking, and previous stroke were also found associated with AD.

The odds of metabolic syndrome were much greater than the sum of the odds of five components in AD. This might mean that the effect of metabolic syndrome, where risk factors coexist, on AD was greater than the sum of the effect of each component. Metabolic syndrome represented a chronic state of inflammation, hyperinsulinemia, dyslipidemia, dysglycemia, vascular injury and oxidative stress, which were linked to AD.[13] Amyloid beta (A β)

deposition initiated an immune response, which was intended to clear the amyloid plaque.[14] However, this response also stimulated the cytokine cascade and reactive oxygen species (ROS), leading to neurodegeneration.[15] Furthermore, inflammatory cascade altered phosphorylation of tau protein along with the oxidative injury to the neurons. The immune response induced by amyloid, in addition to the chronic inflammatory state due to metabolic syndrome, exacerbated the AD pathogenic process, leading to a sufficient etiological factor to progress AD. [16, 17] Metabolic syndrome also induced oxidative stress and increased ROS production. The circulating lipid and glucose imbalance combined with ROS enhances lipoperoxidation, leading to the dysfunction of the antioxidant system. This causes vascular injury and blood-brain barrier (BBB) dysfunction, affecting amyloid and tau accumulation and chronic hypoperfusion, and leads to neuronal damage.[13]

Among components of metabolic syndrome, only high glucose level was found associated with both AD and VD, while others show association only with AD. Many previous studies have reported that diabetes mellitus not only affects cognitive decline but is also associated with a higher risk of cerebrovascular disease including high white matter hyperintensities volume, and cerebral infarcts. Impaired insulin signalling and glucose metabolism in the brain are factors that are related to AD pathogenesis. Insulin modulates A β protein precursor expression and processing.[18] Insulin not only regulates glucose and lipid metabolism in the brain but also regulates neural development and neuronal activities, associated with learning and memory.[19] Insulin receptors are expressed in the brain, particularly in memory registration-related areas, such as the cerebral cortex, hippocampus, hypothalamus, and amygdala.[20] Therefore, impairment of the insulin signalling leads to the pathologic processes of AD. In addition, we assumed that glucose metabolism would be more closely related to the mechanism that caused cognitive impairment after the vascular event. Although previous studies have shown that other vascular risk factors, such as hypertension [21], dyslipidemia [22], and abdominal obesity [23], also increase ischemic stroke. Our study showed that these factors were not associated with VD. Similar to our study, another study showed that high glucose was the most significant component that was associated with cognitive impairment.[24]

The previous stroke is also a factor that affects both AD and VD. The association between stroke and dementia has already been reported in several studies. Ischemic stroke was a risk factor for developing AD and VD.[25, 26] Stroke doubles the risk of dementia and approximately 20% of stroke patients go on to develop cognitive dysfunction within 3 years.[27] Ischemic stroke leads to pathophysiological processes that contribute to ischemic cell damage. Stimulation of the inflammatory process, free radical production, excitotoxicity, disruption of sodium and calcium influx, enzymatic changes, endothelin release, delayed coagulation, activation of platelets and leukocytes, and endothelial dysfunction are the pathophysiological reactions resulting from the onset of stroke.[28] Several studies reported a synergistic relationship between ischemic stroke and AD. Postmortem studies have shown that individuals with AD pathology with cerebral infarction had a markedly increased risk of dementia compared to those with AD pathology without infarcts.[29, 30] Stroke has been suggested as a contributing factor to AD pathological changes including selective brain atrophy and accumulation of abnormal protein such as A β . [31] A previous study also provided evidence that stroke leads to cognitive dysfunction more rapidly in patients with AD.[32] Besides, VD is the severest form of vascular cognitive impairment,[8] and it results from the subclinical vascular brain injury and stroke. Not only major stroke but also minor stroke and even transient ischemic attack are known to increase the risk of dementia.

As per our study, patients with higher BMI were less prone to AD. This result was consistent with so-called obesity paradox that high BMI in the elderly is associated with a lower risk of developing AD. Although obesity is linked to cardiovascular disease, the relationship between obesity and dementia is still not clear, especially in late-life. In previous studies, lower BMI was found associated with A β deposition, tau accumulation and cognitive decline. [33–35] It was also reported that high levels of leptin, a hormone synthesized by adipocytes, enhanced memory function.[36] In the present study, however, patients with obesity were diagnosed with more AD than patients without obesity. Therefore, the trend that patients with higher BMI were less likely to have AD might be because patients with lower BMI had a higher risk of AD.

AD was also found associated with smoking. It is controversial whether smoking has any harmful effect on degenerative diseases. Previously some studies reported that smoking had a protective effect on degenerative diseases.[37–39] There are even researches which have shown that nicotine has a neuroprotective and anti-ageing effect.[40, 41] However, nowadays, smoking has been attributed as a risk factor for Alzheimer's disease.[42] Smoking increases oxidative stress and might have indirect effects on several vascular, inflammatory and degenerative processes.[43, 44] If smoking particles are inhaled, they stimulate ROS production and enters the brain via blood. Smoking-related cerebral oxidative stress is a potential mechanism to accelerate AD pathology and increase risk for AD.[45] Smoking also impairs nitric oxide synthesis in cerebral vascular endothelial cells leading to interference with cerebral blood flow and glucose metabolism in the brain. It induces cerebral hypoperfusion and promotes the synthesis of A β . [46] Smoking stimulates the release of proinflammatory cytokines and immune system-mediated products causing an increase in A β accumulation and tau phosphorylation, hallmarks of the AD pathology.[47]

Our study has some limitations. First, because our study used claim data, we classified the types of dementia, but the actual amyloid burden was unknown. However, in order to distinguish the pure dementia type, those with codes of both AD and VD were excluded. Second, since we only investigated the presence of dementia eight years later, there was no consideration what happened during the eight years and when dementia occurred during the eight years. Besides, there was no consideration for efforts to overcome metabolic syndrome. Some might have tried to treat metabolic syndrome, others might not, but the effect of improvement of metabolic syndrome was not known in our study. Third, it is also a cross-sectional study, there was no consideration for the duration of metabolic syndrome. The association with dementia might vary depending on how long components of metabolic syndrome have been existed, which were not known in our article. Therefore, further longitudinal study is required. Finally, as the cohort only included the specific region of Korea, further investigation in other region or population is needed to generalize these findings.

Despite these limitations, we investigated the effects of metabolic syndrome in different types of dementia and the association between vascular risk factors related to metabolic syndrome and dementia using population-based data. Therefore, we hope to provide new clinical insight into the association between metabolic syndrome and type of dementia with implications for considering different pathophysiology.

Conclusions

Metabolic syndrome was associated with AD, while it was not associated with VD. Therefore, the effect of metabolic syndrome on dementia would be different depending on the type of dementia.

List Of Abbreviation

AD : dementia of the Alzheimer type

VD : vascular dementia

BMI : Body Mass Index

BP : Blood Pressure

TG : triglycerides

HDL-C : high-density lipoprotein cholesterol

NHIS : (Korean) National Health Insurance Service

NHIS-NSC : National Health Insurance Service-National Sample Cohort

ICD-10-CM : International Classification of Disease, Tenth Revision, Clinical Modification

SD : standard deviation

OR : odds ratio

95% CI : 95% confidence interval

A β : amyloid beta

ROS : reactive oxygen species

BBB : blood-brain barrier

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of Chuncheon Sacred Heart Hospital.

Consent for publication

Not applicable

Availability of data and material

The original anonymized data used in this analysis was obtained from NHIS of South Korea. The dataset from NHIS is not publicly available due to restricted access. However, any researcher requiring access to the data can obtain it directly through a license agreement, including the payment of appropriate license fees.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yeo Jin Kim interpreted the data and drafted the manuscript. Sang Mi Kim contributed to the study conceptualization and the discussion of results. Dae Hyun Jeong contributed to the study design and data analysis. Sang-Kyu Lee contributed to the data interpretation and the discussion of results. Moo-Eob Ahn contributed to the study design, data interpretation and the discussion of results. Ohk-Hyun Ryu contributed to the data interpretation, discussion of results and revising the manuscript.

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Not applicable

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Figures

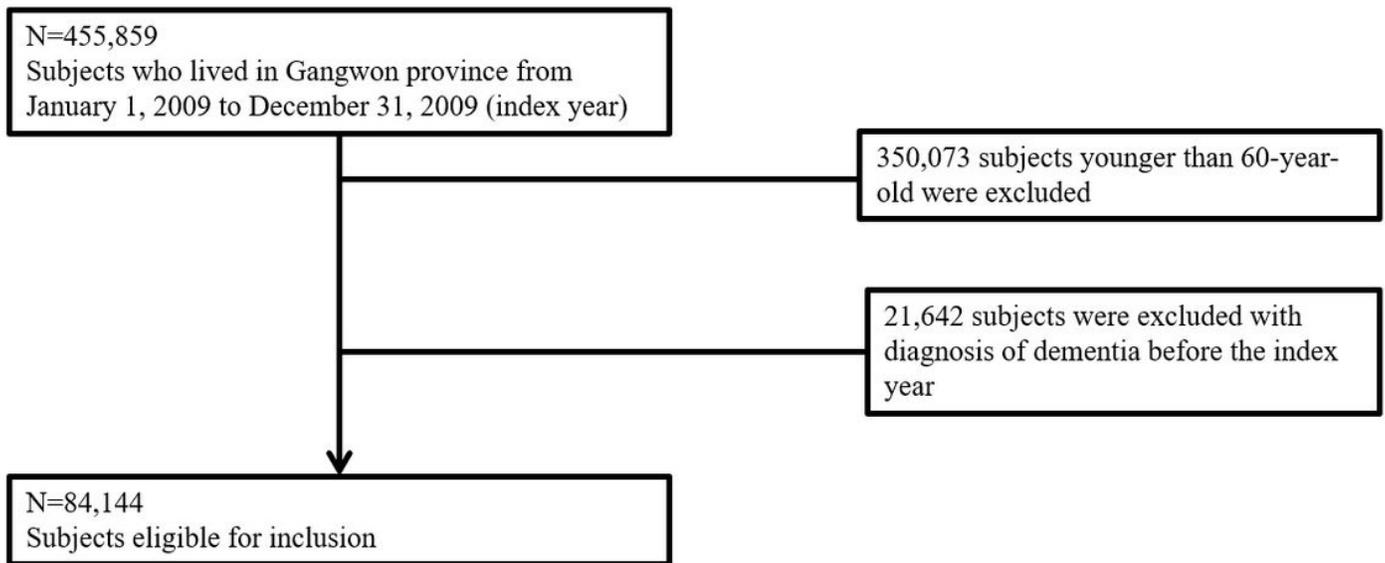


Figure 1

Flow chart of the study population