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Metabolic health, obesity, and incident dementia

Risk of Incident Dementia According to Metabolic Health and Obesity Status in Late-life: a Population-based Cohort Study

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Context: The risk for dementia among obese subjects with normal metabolic profiles, so called metabolically healthy obese (MHO), remains uninvestigated.
Objective: To determine the association between late-life metabolic health and obesity status and risk of incident dementia.
Design: Retrospective cohort study.
Setting: The National Health Insurance System, Republic of Korea.
Patients: 12,296,863 adults over age 50 who underwent health examinations from 2009 to 2012 without baseline history of dementia.
Main Outcome Measure: Incident overall dementia, Alzheimer's disease (AD), and vascular dementia (VaD).
Results: Among population with age ≥60, 363,932 subjects (6.4%) developed dementia during a median follow up of 65 months (interquartile range [IQR] 51-74 months). The MHO group showed the lowest incidence of overall dementia (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.84-0.86) and AD (HR 0.87, 95% CI 0.86-0.88), but not VaD, compared to the metabolically healthy non-obese (MHNO) group. All components of metabolic syndrome except obesity significantly elevated the risk of dementia and these associations were more pronounced in VaD. Particularly, being underweight dramatically increased the risk of dementia.
Conclusions: The MHO phenotype in late life demonstrated decreased risk of overall dementia and AD, but not VaD. Further studies in other populations are warranted to better

understand current results and may serve to predict individuals most at risk of developing dementia.

This large, population-based study analyzed 5,669,488 adults over 60 and found that the metabolically healthy obese phenotype in late life is associated with lower risk of overall dementia. .

Background

As society ages, the prevalence of dementia increases. Currently, 35 million people are suffering from dementia, which is expected to double every 20 years (1, 2). Dementia is characterized by the coexistence of memory impairment and at least one cognitive functional deficit (3). It is also a contributing cause of death, as dementia is usually accompanied by immobility, malnutrition, and weight loss (4). Medical care costs for individuals with dementia are increasing and are substantially greater than those for cancer, heart disease, or other diseases (5).

The most common type of dementia is Alzheimer's disease (AD), which accounts for 60%-80% of cases, followed by vascular dementia (VaD) (6). Aging, family history, apolipoprotein E4 phenotype, and lower educational level are well known risk factors for both AD and VaD (6, 7). In addition, recent evidence suggests both VaD and AD are closely related to cardiovascular risk factors such as hypertension, diabetes mellitus (DM), hyperlipidemia, and cigarette smoking (8-11). Regarding the association between obesity and dementia, midlife obesity is associated with an increased risk of dementia (12, 13), whereas in late life there is a reversed causation (13, 14).

Recently, several studies suggested improvement in clinical outcomes among a subgroup of obese subjects with normal metabolic profiles despite increased adiposity, termed "metabolically healthy obese (MHO)" (15). These subjects exhibited lower insulin resistance, visceral adiposity, and were not at increased risk of cardiovascular disease (CVD) and all-cause mortality compared to metabolically healthy non-obese (MHNO) subjects (15, 16). In contrast, with regard to the development of hypertension, type 2 DM, and chronic kidney disease (CKD), MHO subjects were at 1.4 to 1.6-fold higher risk compared to their non-obese counterparts (17-19). However, to our knowledge, there are no studies reporting the relationship between the MHO phenotype and the development of dementia. Therefore, we investigated the impact of the MHO phenotype on incident dementia according to body mass index (BMI) and metabolic health status, using a nationwide population-based cohort study.

Materials and Methods

Study population

National Health Insurance (NHI) system of Korea consists of the two major programs: NHI (covers 97% of the population) and Medical Aid (MA, covers remaining 3% of the low-income population). All Koreans must be registered in these two systems. Since 2006, database of MA beneficiaries has been integrated into a single National Health Insurance System (NHIS) (20, 21). The NHIS database contains demographic information (age, sex, income level, etc.), claims information (diagnosis defined by International Classification of Diseases [ICD] codes and details of prescriptions), and health check-up information (results of basic laboratory tests and questionnaires about past medical history, current medications, and lifestyle). The national health screening program of NHIS is recommended biannually, and the participation rate is high, recorded 74.8% in 2014 (20-22). In the current study, we used NHIS data, which is an well-established cohort representing the entire Korean population which is over 50 million. This study was approved by the Institutional Review Board of the Yonsei University Health System, Severance Hospital (No. 4-2016-0770) and

informed consent from study participants was waived due to the retrospective cohort nature of the study.

We included subjects who underwent health examinations between January 1, 2009 and December 31, 2012. Of the 23,503,802 adults, subjects who had missing baseline data (n = 195,777), age under 50 (n = 10,926,515), and those who diagnosed with dementia before the index period (n = 84,647) were excluded. A total of 12,296,863 participants were enrolled into the study and were followed for a median of 65 months (interquartile range [IQR] 51-74 months). To determine the association between late-life metabolic health and obesity status and risk of incident dementia, 5,669,488 individuals aged 60 years or older were mainly analyzed and late middle-age group of 50-60 years (n = 6,627,375) was further analyzed in the supplementary analysis.

Clinical and laboratory measurements

As part of the health examinations, all subjects completed a questionnaire on their medical history, use of tobacco and alcohol, and exercise habits. Smoking habits were categorized as non-current or current; alcohol use was classified as <30 g per day or ≥30 g per day (heavy drinker); and exercise level was categorized as <3 times per week or ≥3 times of moderate to vigorous exercise per week (physically active). We defined low socioeconomic status as lowest 20% income status. BMI was calculated as body weight divided by height squared (kg/m^2). Blood pressure (BP) was measured in the sitting position after 5 minutes of rest. After overnight fasting, blood samples were collected. Serum glucose, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured. We calculated glomerular filtration rate (GFR) using the 4-variable Modification of Diet in Renal Disease Study Equation (23). Baseline comorbidities were identified as follows: hypertension (ICD-10 codes I10-13, I15 and treatment with anti-hypertensive medications, or systolic/diastolic BP ≥140/90 mmHg), type 2 DM (ICD-10 codes E11-E14 and anti-diabetic drugs, or fasting glucose level ≥126 mg/dL), hyperlipidemia (ICD-10 code E78 with lipid-lowering agents, or serum total cholesterol ≥240 mg/dL), CKD (eGFR <60 mL/min/1.73m^2), previous myocardial infarction (MI; ICD-10 codes I21-I22) and ischemic stroke (ICD-10 codes I63-I64).

Definition of incident dementia

Incident dementia was considered to be a diagnosis of dementia (ICD-10 codes F00, G30, F01, F02, F03, G23.1, G31.0, G31.1, G31.82, G31.83, G31.88, and F10.7) and prescription of anti-dementia medication at the same time. The anti-dementia medications could include an acetylcholinesterase inhibitor (rivastigmine, galantamine, or aricept) or N-methyl-D-aspartate (NMDA)-receptor antagonist (memantine), which are most commonly used for the treatment of dementia (24). Patients with dementia were grouped into AD (ICD-10 codes F00, G30) or VaD (ICD-10 code F01) by the diagnosis code at the first visit. If both diagnosis of AD and VaD were recorded at the first visit, we used the diagnosis of the second visit.

Definitions of metabolic health and obesity status

Obesity phenotypes were based on the Asia-Pacific BMI criteria (non-obese <25 kg/m^2 or obese ≥25 kg/m^2), which were established by the World Health Organization Western Pacific Region (25). To identify an individual as metabolically healthy, we used the Adult Treatment Panel-III (ATP-III) definition (26). The waist circumference (WC) criterion was not used due to its collinearity with BMI by adopting the definition of previous studies (19, 27). Metabolically healthy was defined as meeting no more than one of the following four criteria: 1) a systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg, or on anti-hypertensive treatment; 2) TG ≥150 mg/dL; 3) fasting plasma glucose (FPG) ≥100 mg/dL or on antidiabetic treatment; 4) HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women.

According to these criteria, participants were categorized as follows: 1) MHNO: BMI <25 kg/m^2 and <2 metabolic risk factors; 2) metabolically unhealthy non-obese (MUNO): BMI <25 kg/m^2 and ≥2 metabolic risk factors; 3) MHO: BMI ≥25 kg/m^2 and <2 metabolic risk factors; 4) metabolically unhealthy obese (MUO): BMI ≥25 kg/m^2 and ≥2 metabolic risk factors.

Statistical analysis

All continuous variables are expressed as a mean (standard deviation), and categorical data are presented as numbers (percentages). The characteristics of study participants according to metabolic health and obesity status were compared using one-way analysis of variance for continuous variables and the chi-square test for categorical variables. Dementia-free survival curves were constructed using the Kaplan-Meier method, and between-group differences were compared using log-rank tests. Person-years of follow-up were calculated from the date of the health examination to the date of diagnosis of dementia or to December 31, 2016, whichever came first. Multivariate Cox proportional hazards regression analysis was performed to identify hazard ratios (HRs) of incident dementia according to metabolic health and obesity status: unadjusted in model 1, age and sex were adjusted in model 2, and tobacco and alcohol use, exercise habits, socioeconomic status, and LDL-cholesterol were further adjusted in model 3. The MHNO group was used as a reference, and results are presented as HR and 95% confidence interval (CI). Subgroup analyses were conducted by dividing the subjects according to the status of smoking, drinking, and exercise to adjust for the influence of modifiable risk factors, which were different in the baseline profiles among the four groups. We also conducted supplementary analyses: First, as being underweight is associated with vitamins and mineral deficiencies and as undetected subtle dementia may cause body weight loss, sensitivity analyses were conducted after exclusion of individuals with BMI under 18.5 kg/m^2. Second, given the increasing incidence of dementia in younger individuals, we further analyzed the effect of metabolic health and obesity status on the development of dementia in subjects aged 50-60 years. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and R programming version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria, http:www.R-project.org). A P-value <0.05 was considered significant.

Results

Baseline characteristics of study subjects

The baseline clinical and biochemical characteristics of the subjects are summarized in Table 1. Among 5,669,488 participants aged over 60, 1,738,074 (30.7%), 1,852,845 (32.7%), 644,447 (11.4%), and 1,434,122 (25.3%) were categorized into the MHNO, MUNO, MHO, and MUO groups, respectively. The mean age was 67.1 years, 45.7% were male, and mean BMI was 24.1 kg/m^2.

Figure 1 shows the distribution by ATP-III criteria for metabolic syndrome in the four groups. All parameters showed higher prevalence in the metabolically unhealthy groups than in the metabolically healthy groups. Of these, the most common ATP-III criterion for metabolic syndrome was high blood pressure (69.3%), followed by hyperglycemia (54.8%), hypertriglyceridemia (49.2%), and low HDL cholesterol (43.6%).

Risk of incident dementia according to metabolic health and obesity status

During 29,089,302 person-years of follow-up, a total of 363,932 subjects (6.4%) developed incident dementia. Among them, 267,368 (73.5%) had AD and 43,918 (12.1%) had VaD. The crude incidence rate of overall dementia was 5.7% (99,538/1,738,074) in the MHNO group, 8.1% (150,341/1,852,845) in the MUNO group, 4.3% (27,675/644,447) in the MHO group, and 6.0% (86,378/1,434,122) in the MUO group. Figure 2 shows the Kaplan-Meier curves for

overall dementia-free survival for each group. Individuals in the MHO group had the lowest probabilities of developing incident dementia, and the probabilities increased sequentially for the MHNO, MUO, and MUNO group (log rank p<0.001).

The incidence rates (number of events per 1,000 person-years) and HRs of overall dementia, AD, and VaD according to metabolic health and obesity status are demonstrated in Table 2. Adjusted HR (95% CI) of the MUNO, MHO, and MUO groups for incident overall dementia were 1.16 (1.15-1.17), 0.85 (0.84-0.86), and 1.01 (0.99-1.02) compared with MHNO group after adjustment for age, sex, tobacco and alcohol use, exercise level, socioeconomic status, and LDL-cholesterol (model 3). With regard to the subtypes of dementia, subjects in the MHO group showed a significantly lower HR for AD, compared with the MHNO group; however, a protective effect was not observed in VaD. In addition, those who were metabolically unhealthy were associated with increased dementia risk, and this effect was more prominent in VaD than AD, demonstrating a 30%-40% risk elevation. There was no gender-related difference in the incidence of dementia (data not shown).

Furthermore, we conducted subgroup analyses by dividing the subjects according to smoking, drinking, and exercise status: (1) subjects without modifiable risk factors (both non-current smoker, no heavy drinker, and physically active; n = 1,978,111) and (2) subjects with modifiable risk factors (both current smoker, heavy drinker, and not physically active; n = 60,564). Consistent with the main results, the MHO group showed the lowest incidence of overall dementia and AD; incident VaD was not affected, regardless of the presence of modifiable risk factors (Table 3). In particular, the protective effect of the MHO on the development of AD was more prominent in the dementia-prone individuals with risk factors (HR 0.71 in the group with risk factors vs. 0.88 in the group with no risk factors).

Impact of metabolic syndrome and its components on the risk of incident dementia

Next, we examined the association between BMI, components of metabolic syndrome, and incident dementia (Table 4). Compared with non-obese subjects, obese individuals had decreased risk of overall dementia (HR 0.90, 95% CI 0.89-0.91) and AD (HR 0.88, 95% CI 0.87-0.89), but obesity had no beneficial impact on VaD (HR 1.01, 95% CI 0.99-1.03). All metabolic syndrome criteria (high BP, hyperglycemia, high triglyceride, and low HDL cholesterol) were significantly associated with the development of dementia regardless of type, and these associations were more pronounced in VaD. Meeting 2 or more criteria for metabolic syndrome was also highly correlated with the development of overall dementia, and the adjusted HR was significantly higher in VaD compared to AD (HR 1.37 vs 1.14).

Supplementary analyses

A sensitivity analysis (exclusion of underweight subjects with BMI <18.5 kg/m^2) revealed that the MHO group showed decreased risks of overall dementia and AD, but lost statistical significance in VaD (Table 5). However, the risk of dementia was increased in the MUO group, while it decreased in the MUNO group, suggesting that being underweight contributes significantly to the development of dementia.

Similar patterns were noted for subjects aged 50-60 years (n = 6,627,375), although the protective effect of MHO phenotype on overall dementia was smaller than that in subjects aged over 60 (Table 6, 7). Additionally, the MUO group of individuals aged 50-60 years showed a much higher risk of VaD than those aged over 60 years (HR 1.71 vs 1.33), suggesting that metabolic abnormalities have a greater impact on the incidence of dementia in middle-aged individuals.

Discussion

In this longitudinal nationwide study, we analyzed the risk of incident dementia according to late-life metabolic health and obesity status. Among four groups, subjects with MHO showed

the lowest incidences of overall dementia and AD but had no impact on the development of VaD. Furthermore, the protective effect of the MHO on AD was maintained in both high risk and low risk group, excluding underweight subjects, and in middle-age individuals, although the degree was different. Of component, unhealthy metabolic profiles were positively associated with incident dementia, particularly in VaD, and obesity was associated with lower risk on the development of AD.

With respect to the impact of metabolic status on dementia, our study revealed that having two or more metabolic abnormalities was associated with development of both AD and VaD. This effect was more prominent in VaD, with a 41% greater risk in MUNO subjects compared to non-obese MHNO subjects, and a 31% greater risk in MUO subjects compared to non-obese MHO subjects. Furthermore, all criteria for metabolic syndrome (high BP, high glycemia, high triglycerides and low HDL cholesterol) were associated with an increased risk of incident dementia.

Hypertension is reported to increase the risk of incident VaD 2.0 to 4.6-fold in female subjects but the HR in male subjects was not statistically significant (28, 29). However, a meta-analysis of six longitudinal studies demonstrated that hypertension is associated with VaD (odds ratio 1.59, 95% CI 1.29-1.95) (30). Our findings are consistent with the latter that high BP is associated with VaD (HR 1.44, 95% CI 1.41-1.48). DM is also a well-known risk factor for incident dementia, increasing risk 1.5 to 2.0-fold; the impact was evident in the development of VaD, showing a HR of 2.0-2.5, but its relationship to AD was not consistent (31-34). In our study, hyperglycemia increased the risk of overall dementia and AD 1.2-fold, and raised the risk of VaD 1.3-fold. The impact on VaD was less than expected, probably because we defined hyperglycemia as including both prediabetes and diabetes (either FPG $\geq$100 mg/dL or on antidiabetic treatment), while previous studies were conducted in only patients with diabetes. Regarding hyperlipidemia and dementia, the published findings are inconsistent (34-37). However, in our large-scale analyses, both high triglycerides and low HDL cholesterol were associated with a 6%-16% increased risk of dementia. The inconsistent results may be explained by differences in study design, such as age or ethnicity of participants, and different definitions of hyperlipidemia.

Previous studies investigating the association between obesity and the development of dementia reported that midlife obesity was associated with a 1.7 to 2.0-fold increased risk of incident dementia (12, 38). In contrast, most recent studies revealed that being overweight or obese in old age is protective for dementia development (13, 14, 39-41). Regarding mortality, overweight subjects with AD showed a longer survival compared to those with normal weight (42). Our study results are in line with previous study results showing significant risk reduction of AD in old obese subjects. These results are consistent with the hypothesis of the 'obesity paradox' in which overweight or obese subjects are predicted to have lower mortality than normal weight subjects in various established disease cohorts (43-45). When we further analyzed the effect of metabolic health and obesity status on the development of dementia in subjects aged 50-60 years, the MHO group consistently demonstrated the lowest incidence of overall dementia and AD, but to a lesser extent than that in subjects aged 60 years and older. In addition, when underweight subjects were excluded in the analysis, the risk of dementia increased in the MUO group, whereas the risk in the MUNO group decreased, suggesting that being underweight had a great impact on the incidence of dementia.

There are several possible mechanisms explaining the beneficial role of MHO regarding development of dementia. First, unintentional weight loss in the elderly is usually associated with malnutrition and coexisting chronic diseases (46). Actually, many studies have demonstrated that weight loss precedes the diagnosis of dementia by 10 years (47, 48). Second, plasma insulin-like growth factor I (IGF-1) levels decline in the underweight group

(49). By exerting neurotrophic activities in the hippocampus, it is associated with better cognitive performance (50), and decreased serum IFG-1 level turned out to be an independent risk factor for AD and VaD (51). Third, adipokines secreted from adipose tissue may play a role (52). A higher circulating leptin level is associated with a higher cerebral brain volume, including the hippocampus, and is inversely correlated with cognitive impairment and incident dementia (53, 54). Fourth, persistent organic pollutants (POPs) such as polychlorinated biphenyls or polychlorinated dibenzofurans have been reported to cause various toxic effects, especially in neurocognitive function (55, 56). Exposure to POPs was associated with dose-dependent deterioration of attention, memory and learning ability (57, 58), which suggests potential links to dementia. As POPs are usually lipophilic and are distributed in adipose tissue, serum concentrations increase after weight loss with redistribution to tissues such as brain (59) .

Our study has several limitations. First, dementia and other comorbidities were identified using claims data from the NHIS database. There is a possibility of coding errors or under- or over-estimation. To avoid overestimation and to raise diagnostic accuracy, we defined dementia using both ICD-10 codes and history of prescription anti-dementia drugs. The incidence rate of overall dementia (12.5 per 1000 person-years) reported in this study is consistent to the rates reported in previous studies in China, Japan, and Europe (60-62), which raise reliability of our study. Second, BMI or metabolic status can change over time in a substantial proportion of the population, however, our study did not reflect the longitudinal changes of body weight or laboratory findings. Third, as the mean BMI of MHO group was 27.0 kg/m^2, the study results may not be generalized to a more severely obese group. Fourth, despite this longitudinal study design, our findings cannot be used to make causal inferences. Further prospective are needed to determine metabolic health and obesity status as predisposing factors for dementia. Fifth, the information about apolipoprotein E4 phenotype, educational level, vitamin B12 and vitamin D status, and thyroid function test was not available. Despite these limitations, this is the first study to investigate the risk of incident dementia among different metabolic phenotypes in older adults. We analyzed a nationwide population over 29,089,304 person-years of follow-up. The large sample size provided statistical power to demonstrate associations between metabolic health and obesity status and dementia.

In summary, the present study illustrated different risks for dementia according to metabolic health and obesity status in late life using an Asian population-based cohort. The MHO phenotype showed a 13-15% lower risk of overall dementia and AD, compared to the MHNO phenotype, but no difference in the incidence of VaD. Increased dementia incidence in the metabolically unhealthy group was more prominent in VaD and risk reduction in obese group was evident in AD. Further studies in other populations are warranted, to better understand the effect of metabolic health status and obesity on dementia.

Abbreviations

AD: Alzheimer's disease; ATP-III: Adult Treatment Panel-III; BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; CVD: Cardiovascular disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; FPG: Fasting plasma glucose; GFR: Glomerular filtration rate; HDL: High-density lipoprotein; HR: Hazard ratio; ICD: International Classification of Diseases; IGF-1: Insulin-like growth factor I; IQR: Interquartile range; LDL: Low-density lipoprotein; MI: Myocardial infarction; MHNO: Metabolically healthy non-obese; MHO: Metabolically healthy obese; MUNO: Metabolically unhealthy non-obese; MUO: Metabolically unhealthy obese; NHIS: National Health Insurance System; POPs: Persistent organic pollutants; TG: Triglyceride; VaD: Vascular dementia; WC: Waist circumference

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Figure 1. Distribution of metabolic syndrome criteria by metabolic health and obesity status. Abbreviations: BP, blood pressure; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

Figure 2. Dementia-free survival by Kaplan-Meier. A. Overall dementia. B. Alzheimer's disease. C. Vascular dementia. Subjects were followed for a median of 65 months (interquartile range 51-74 months). Cumulative dementia-free probability is presented in the y-axis. Plots use different y-axis scale. Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

Table 1. Baseline characteristics of study subjects according to metabolic healthy and obesity

Characteristic	Non-obese (n = 3,590,919)		Obese (n = 2,078,569)	
	MHNO (n = 1,738,074)	MUNO (n = 1,852,845)	MHO (n = 644,447)	MUO (n = 1,434,122)
Age, y	66.8 ± 6.4	68.1 ± 6.8	65.8 ± 5.6	66.9 ± 6.0
Male sex	867,637 (49.9)	865,703 (46.7)	263,261 (40.9)	595,782 (41.5)
Height, cm	158.9 ± 8.6	158.3 ± 8.8	157.7 ± 8.6	157.8 ± 8.8
Weight, kg	55.6 ± 7.9	56.8 ± 8.0	67.3 ± 8.1	68.4 ± 8.6
BMI, kg/m^2	22.0 ± 2.0	22.6 ± 1.8	27.0 ± 1.8	27.4 ± 2.1
Systolic BP, mmHg	122.3 ± 14.8	132.0 ± 15.6	126.1 ± 14.7	133.6 ± 15.2
Diastolic BP, mmHg	75.0 ± 9.5	79.4 ± 9.9	77.2 ± 9.5	80.5 ± 9.8
Fasting glucose, mg/dL	92.8 ± 16.0	111.0 ± 30.9	93.1 ± 14.4	112.0 ± 29.6
Total cholesterol, mg/dL	196.6 ± 36.2	197.5 ± 40.4	201.6 ± 36.9	200.4 ± 40.6
Triglyceride, mg/dL	98.3 ± 42.5	163.2 ± 93.9	106.4 ± 43.7	175.2 ± 95.4
HDL-C, mg/dL	59.0 ± 17.7	50.3 ± 17.7	57.7 ± 17.3	49.2 ± 17.0
LDL-C, mg/dL	118.2 ± 33.4	115.4 ± 36.9	122.8 ± 34.3	117.1 ± 37.4
Current smoker	285,388 (16.4)	293,240 (15.8)	59,865 (9.3)	150,405 (10.5)
Heavy drinker	68,470 (3.9)	92,641 (5.0)	20,785 (3.2)	61,843 (4.3)
Exercise	759,858 (43.7)	750,817 (40.5)	284,349 (44.1)	585,875 (40.9)
Low SES	384,236 (22.1)	414,186 (22.4)	139,787 (21.7)	315,948 (22.0)
Comorbidities				
Hypertension	484,857 (27.9)	1,234,184 (66.6)	262,942 (40.8)	1,086,237 (75.7)
Diabetes	75,192 (4.3)	539,691 (29.1)	26,257 (4.1)	469,584 (32.7)
Hyperlipidemia	149,566 (8.6)	253,593 (13.7)	67,287 (10.4)	212,404 (14.8)
CKD	162,082 (9.3)	285,461 (15.4)	72,966 (11.3)	247,832 (17.3)
Previous myocardial infarction	77,872 (4.5)	127,374 (6.9)	37,534 (5.8)	116,146 (8.1)
Previous ischemic stroke	80,878 (4.7)	144,502 (7.8)	33,838 (5.3)	111,809 (7.8)

Values are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables.
Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; BMI, body mass index; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SES, socioeconomic status; CKD, chronic kidney disease

Table 2. Hazard ratios for the development of dementia according to metabolic health and obesity status

Group	Incident cases, n	Person-years, n	Incident rate*	Model 1†	Model 2‡	Model 3§
Overall dementia						
MHNO	99,538	8,928,576	11.1	1 (ref)	1 (ref)	1 (ref)
MUNO	150,341	9,386,923	16.0	**1.44 (1.43-1.45)**	**1.20 (1.19-1.21)**	**1.16 (1.15-1.17)**
MHO	27,675	3,364,116	8.2	**0.74 (0.73-0.75)**	**0.86 (0.84-0.87)**	**0.85 (0.84-0.86)**
MUO	86,378	7,409,687	11.7	**1.05 (1.04-1.06)**	**1.04 (1.03-1.05)**	1.01 (0.99-1.02)
Alzheimer's disease						
MHNO	74,340	8,928,576	8.3	1 (ref)	1 (ref)	1 (ref)
MUNO	110,318	9,386,923	11.8	**1.41 (1.40-1.43)**	**1.16 (1.15-1.18)**	**1.38 (1.35-1.42)**
MHO	20,254	3,364,116	6.0	**0.72 (0.71-0.73)**	**0.84 (0.83-0.85)**	**0.87 (0.86-0.88)**
MUO	62,456	7,409,687	8.4	1.01 (1.00-1.02)	1.00 (0.99-1.02)	**1.29 (1.25-1.32)**
Vascular dementia						
MHNO	10,701	8,928,576	1.2	1 (ref)	1 (ref)	1 (ref)
MUNO	18,235	9,386,923	1.9	**1.62 (1.59-1.66)**	**1.42 (1.38-1.45)**	**1.41 (1.38-1.44)**
MHO	3,487	3,364,116	1.0	**0.86 (0.83-0.90)**	0.99 (0.96-1.03)	1.02 (0.98-1.06)
MUO	11,495	7,409,687	1.6	**1.29 (1.26-1.33)**	**1.32 (1.28-1.35)**	**1.33 (1.29-1.36)**

Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese
*Incident rate for 1000 person-years
†Unadjusted
‡Adjusted for age and sex
§Further adjusted for tobacco and alcohol use, exercise, socioeconomic status, and low density lipoprotein-cholesterol
Values with statistical significance are printed in bold.

Table 3. Contribution of metabolic health and obesity status on the development of dementia according to the presence of modifiable risk factors

Group	Without modifiable risk factors*		With modifiable risk factors†	
	Model 1‡	Model 2§	Model 1‡	Model 2§
Overall dementia				
MHNO	1 (ref)	1 (ref)	1 (ref)	1 (ref)
MUNO	**1.07 (1.06-1.09)**	**1.05 (1.03-1.07)**	**0.77 (0.68-0.86)**	1.00 (0.89-1.12)
MHO	**0.79 (0.77-0.81)**	**0.89 (0.87-0.92)**	**0.65 (0.53-0.79)**	**0.81 (0.67-0.98)**
MUO	**1.42 (1.40-1.44)**	**1.18 (1.16-1.20)**	**1.23 (1.14-1.33)**	**1.32 (1.23-1.43)**
Alzheimer's disease				
MHNO	1 (ref)	1 (ref)	1 (ref)	1 (ref)
MUNO	**1.03 (1.01-1.05)**	1.00 (0.98-1.03)	**0.75 (0.65-0.86)**	1.00 (0.87-1.15)
MHO	**0.78 (0.76-0.80)**	**0.88 (0.86-0.91)**	**0.55 (0.43-0.71)**	**0.71 (0.55-0.91)**
MUO	**1.39 (1.37-1.42)**	**1.15 (1.13-1.17)**	**1.17 (1.06-1.28)**	**1.26 (1.15-1.38)**
Vascular dementia				
MHNO	1 (ref)	1 (ref)	1 (ref)	1 (ref)
MUNO	**1.41 (1.34-1.48)**	**1.39 (1.32-1.46)**	0.97 (0.74-1.27)	1.19 (0.91-1.56)
MHO	0.97 (0.90-1.04)	1.07 (1.00-1.15)	0.77 (0.48-1.22)	0.91 (0.57-1.45)
MUO	**1.66 (1.58-1.74)**	**1.43 (1.37-1.51)**	**1.44 (1.19-1.75)**	**1.52 (1.25-1.85)**

Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese
* Subjects of both non-current smoker, not heavy drinker, and physically active
† Subjects of both current smoker, heavy drinker, and not physically active
‡ Unadjusted
§ Adjusted for age, sex, socioeconomic status, and low density lipoprotein-cholesterol
Values with statistical significance are printed in bold.

Table 4. Hazard ratios for developing dementia according to obesity status and metabolic syndrome criteria

Criteria	Overall dementia		Alzheimer's disease		Vascular dementia	
	n	Adjusted HR* (95% CI)	n	Adjusted HR* (95% CI)	n	Adjusted HR* (95% CI)
Obesity†						
No (n = 3,590,919)	249,879	1 (ref)	184,658	1 (ref)	28,936	1 (ref)
Yes (n = 2,078,569)	114,053	**0.90 (0.89-0.91)**	82,710	**0.88 (0.87-0.89)**	14,982	1.01 (0.99-1.03)
High blood pressure‡						
No (n = 1,737,573)	86,464	1 (ref)	65,197	1 (ref)	8,800	1 (ref)
Yes (n = 3,931,915)	277,468	**1.10 (1.09-1.11)**	202,171	**1.05 (1.04-1.06)**	35,118	**1.44 (1.41-1.48)**
Hyperglycemia§						
No (n = 3,053,488)	178,572	1 (ref)	132,326	1 (ref)	20,711	1 (ref)
Yes (n = 2,616,000)	185,360	**1.21 (1.20-1.22)**	135,042	**1.19 (1.18-1.20)**	23,207	**1.30 (1.28-1.33)**
High triglycerides‖						
No (n = 3,807,141)	238,245	1 (ref)	175,715	1 (ref)	28,040	1 (ref)
Yes (n = 1,862,347)	125,687	**1.07 (1.06-1.08)**	91,653	**1.06 (1.05-1.07)**	15,878	**1.15 (1.13-1.17)**
Low HDL cholesterol						
No (n = 4,059,350)	239,860	1 (ref)	175,794	1 (ref)	29,029	1 (ref)
Yes (n = 1,610,138)	124,072	**1.08 (1.07-1.09)**	91,574	**1.07 (1.06-1.08)**	14,889	**1.16 (1.14-1.18)**
Metabolic syndrome**						
No (n = 2,382,521)	127,213	1 (ref)	94,594	1 (ref)	14,188	1 (ref)
Yes (n = 3,286,967)	236,719	**1.18 (1.17-1.19)**	172,774	**1.14 (1.13-1.15)**	29,730	**1.37 (1.35-1.40)**

Abbreviations: HR, hazard ratio; CI, confidence interval

*Adjusted for age, sex, tobacco and alcohol use, exercise, and socioeconomic status

†Body mass index (BMI) ≥ 25 kg/m^2

‡Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on antihypertensive medication

§Fasting plasma glucose ≥ 100 mg/dL or on anti-diabetic medication

‖Triglycerides ≥ 150 mg/dL

¶High-density lipoprotein cholesterol <40 mg/dL in males or <50 mg/dL in females

**Meet 2 or more of metabolic syndrome criteria

Values with statistical significance are printed in bold.

Table 5. Sensitivity analysis for the development of dementia after exclusion of underweight individuals

Group	Incident cases, n	Person-years, n	Incident rate*	Model 1†	Model 2‡	Model 3§
Overall dementia						
MHNO	88,406	8,401,410	10.5	1 (ref)	1 (ref)	1 (ref)
MUNO	141,267	9,128,208	15.5	**1.11 (1.10-1.12)**	**1.07 (1.06-1.08)**	**1.07 (1.06-1.08)**
MHO	27,675	3,364,116	8.2	**0.78 (0.77-0.79)**	**0.88 (0.87-0.89)**	**0.88 (0.88-0.90)**
MUO	86,378	7,409,687	11.7	**1.47 (1.46-1.49)**	**1.21 (1.20-1.22)**	**1.21 (1.20-1.22)**
Alzheimer's disease						
MHNO	65,867	8,401,410	7.8	1 (ref)	1 (ref)	1 (ref)
MUNO	103,566	9,128,208	11.3	**1.08 (1.06-1.09)**	**1.03 (1.02-1.04)**	**1.03 (1.02-1.04)**
MHO	20,254	3,364,116	6.0	**0.77 (0.76-0.78)**	**0.86 (0.85-0.88)**	**0.87 (0.86-0.88)**
MUO	62,456	7,409,687	8.4	**1.45 (1.44-1.47)**	**1.18 (1.17-1.19)**	**1.17 (1.16-1.19)**
Vascular dementia						
MHNO	9643	8,401,410	1.2	1 (ref)	1 (ref)	1 (ref)
MUNO	17,282	9,128,208	1.9	**1.35 (1.32-1.39)**	**1.34 (1.30-1.38)**	**1.35 (1.31-1.38)**
MHO	3487	3,364,116	1.0	**0.90 (0.87-0.94)**	1.01 (0.97-1.05)	1.03 (0.99-1.07)
MUO	11,495	7,409,687	1.6	**1.65 (1.61-1.69)**	**1.42 (1.39-1.46)**	**1.42 (1.38-1.45)**

Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese

*Incident rate for 1000 person-years

†Unadjusted

‡Adjusted for age and sex

§Further adjusted for tobacco and alcohol use, exercise, socioeconomic status, and low density lipoprotein-cholesterol

Values with statistical significance are printed in bold.

Table 6. Baseline characteristics of study subjects according to metabolic healthy and obesity in subjects aged 50-60 years

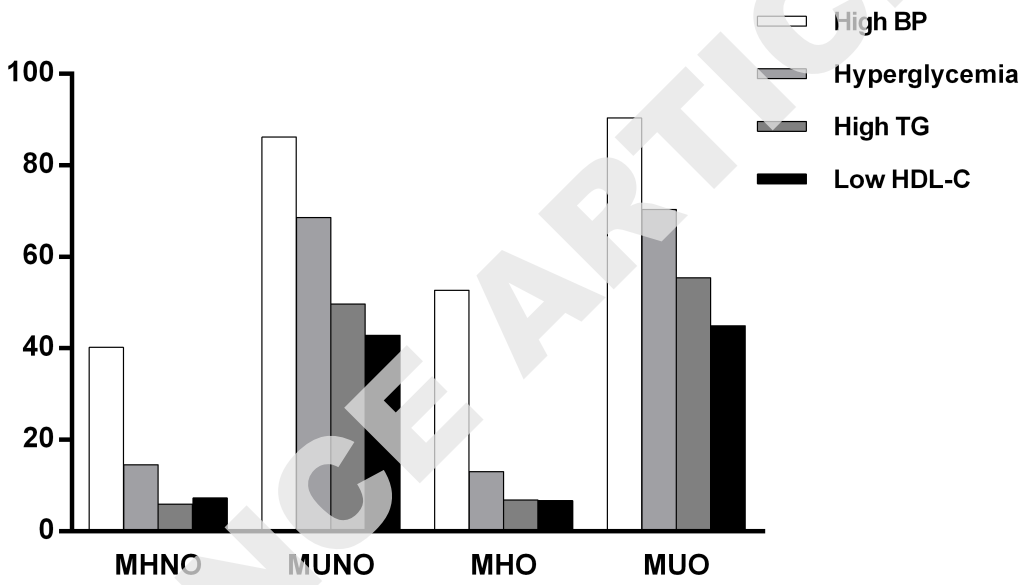
Characteristic	Non-obese (n = 4,270,579)		Obese (n = 2,356,796)	
	MHNO (n = 3,282,724)	MUNO (n = 987,855)	MHO (n = 1,024,260)	MUO (n = 1,332,536)
Age, y	53.5 ± 3.3	54.6 ± 3.4	53.7 ± 3.3	54.4 ± 3.4
Male sex	1,468,731 (44.7)	454,427 (46.0)	546,028 (53.3)	695,994 (52.2)
Height, cm	161.5 ± 8.0	161.6 ± 8.2	161.9 ± 8.4	162.3 ± 8.7
Weight, kg	58.1 ± 7.6	60.4 ± 7.5	70.2 ± 8.0	72.9 ± 9.2
BMI, kg/m^2	22.2 ± 1.8	23.1 ± 1.5	26.78 ± 1.7	27.6 ± 2.2
Systolic BP, mmHg	119.5 ± 14.1	128.9 ± 14.8	123.3 ± 13.8	131.0 ± 14.6
Diastolic BP, mmHg	74.9 ± 9.7	80.2 ± 10.0	77.4 ± 9.6	81.8 ± 9.9
Fasting glucose, mg/dL	94.9 ± 19.1	112.8 ± 34.7	95.3 ± 17.2	111.8 ± 31.4
Total cholesterol, mg/dL	200.0 ± 34.5	205.9 ± 43.8	204.2 ± 34.2	206.4 ± 41.5
Triglyceride, mg/dL	98.1 ± 17.2	161.2 ± 18.9	109.8 ± 18.2	169.4 ± 18.8
HDL-C, mg/dL	58.3 ± 15.7	51.1 ± 16.2	55.6 ± 15.4	49.6 ± 15.8
LDL-C, mg/dL	119.9 ± 31.9	118.9 ± 41.1	124.5 ± 31.8	119.5 ± 38.9
Current smoker	675,096 (20.6)	222,377 (22.5)	186,371 (18.2)	273,367 (20.5)
Heavy drinker	174,917 (5.3)	74,104 (7.5)	67,816 (6.6)	117,302 (8.8)
Exercise	1,688,721 (51.4)	490,834 (49.7)	540,187 (52.7)	658,377 (49.4)
Low SES	723,132 (22.0)	227,418 (23.0)	215,868 (21.1)	299,117 (22.5)
Comorbidities				
Hypertension	569,118 (17.3)	541,839 (54.9)	256,199 (25.0)	821,072 (61.6)
Diabetes	154,171 (4.7)	256,067 (25.9)	48,092 (4.7)	341,823 (25.7)
Hyperlipidemia	458,779 (14.0)	539,040 (54.6)	155,503 (15.2)	638,897 (48.0)
CKD	111,024 (3.4)	52,927 (5.4)	36,746 (3.6)	70,943 (5.3)
Previous myocardial infarction	40,662 (1.2)	40,868 (4.1)	14,702 (1.4)	55,136 (4.1)
Previous ischemic stroke	41,234 (1.3)	35,804 (3.6)	14,855 (1.4)	45,748 (3.4)

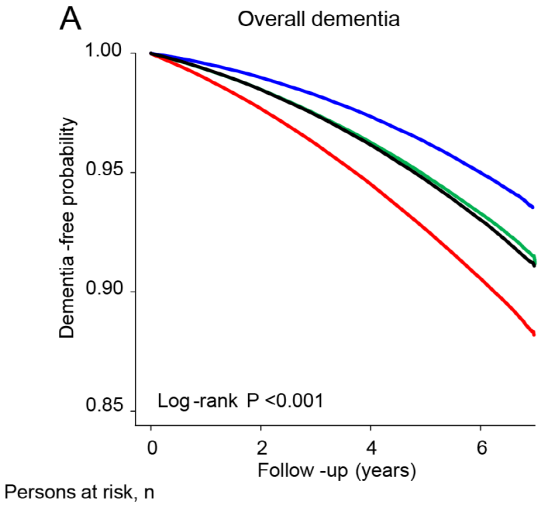
Values are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables.
Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; BMI, body mass index; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SES, socioeconomic status; CKD, chronic kidney disease

Table 7. Hazard ratios for the development of dementia according to metabolic health and obesity status in subjects aged 50-60 years

Group	Incident cases, n	Person-years, n	Incident rate*	Model 1†	Model 2‡	Model 3§
Overall dementia						
MHNO	12,678	17,056,868	0.7	1 (ref)	1 (ref)	1 (ref)
MUNO	6611	5,171,781	1.3	**1.38 (1.34-1.43)**	**1.19 (1.16-1.23)**	**1.19 (1.16-1.23)**
MHO	3601	5,356,227	0.7	**0.90 (0.87-0.94)**	**0.88 (0.85-0.91)**	**0.90 (0.87-0.93)**
MUO	7188	6,962,901	1.0	**1.71 (1.66-1.76)**	**1.42 (1.28-1.46)**	**1.41 (1.37-1.45)**
Alzheimer's disease						
MHNO	7903	17,056,868	0.5	1 (ref)	1 (ref)	1 (ref)
MUNO	3967	5,171,781	0.8	**1.31 (1.26-1.36)**	**1.11 (1.07-1.16)**	**1.11 (1.07-1.16)**
MHO	2184	5,356,227	0.4	**0.88 (0.84-0.92)**	**0.86 (0.82-0.90)**	**0.88 (0.83-0.92)**
MUO	4252	6,962,901	0.6	**1.65 (1.58-1.71)**	**1.33 (1.28-1.38)**	**1.33 (1.28-1.38)**
Vascular dementia						
MHNO	2437	17,056,868	0.1	1 (ref)	1 (ref)	1 (ref)
MUNO	1467	5,171,781	0.3	**1.72 (1.61-1.83)**	**1.52 (1.43-1.62)**	**1.53 (1.44-1.63)**
MHO	769	5,356,227	0.1	1.00 (0.92-1.08)	0.97 (0.89-1.05)	0.99 (0.92-1.08)
MUO	1713	6,962,901	0.2	**1.98 (1.85-2.11)**	**1.73 (1.62-1.84)**	**1.71 (1.60-1.82)**

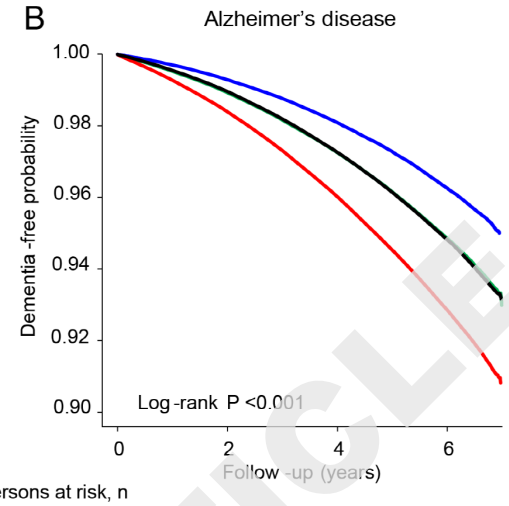
Abbreviations: MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese
*Incident rate for 1000 person-years
†Unadjusted
‡Adjusted for age and sex
§Further adjusted for tobacco and alcohol use, exercise, socioeconomic status, and low density lipoprotein-cholesterol
Values with statistical significance are printed in bold.





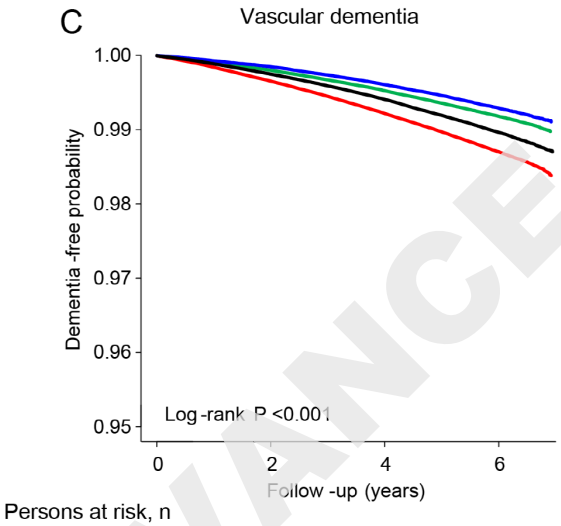
Persons at risk, n

MHNO	99538	73341	37111	5145
MUNO	150341	107775	52922	7076
MHO	27675	21079	11043	1569
MUO	86378	64362	32725	4549



Persons at risk, n

MHNO	74340	55952	29102	4264
MUNO	110318	81143	40912	5707
MHO	20254	15654	8421	1261
MUO	62456	47561	24776	3601



Persons at risk, n

MHNO	10701	7599	3696	496
MUNO	16235	12467	5830	778
MHO	3487	2591	1291	117
MUO	11495	8227	4081	563