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## Factors Predicting the Onset of Amnesic Mild Cognitive Impairment or Alzheimer’s Dementia in Persons With Subjective Cognitive Decline

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### Abstract

The objective of the current retrospective cohort study was to identify vascular and/or neuropsychiatric risk factors predicting clinical progression in persons with subjective cognitive decline (SCD). Information on 1,525 persons with SCD (mean age = 73.8 [ $SD = 8.1$ ] years) was obtained from the National Alzheimer’s Coordinating Center. Clinical progression occurred from SCD to either amnesic mild cognitive impairment or Alzheimer’s dementia over an average of 4.7 ( $SD = 2.9$ ) years. Stepwise Cox regression was used. Compared to obesity (hazard ratio [HR] = 0.59) in the univariate unadjusted model, obesity (HR = 0.64), current smoking (HR = 2.02), and depressive symptoms (HR = 1.35) were significant after adjusting for covariates in the univariate model. In the multivariate adjusted model, obesity (HR = 0.64), current smoking (HR = 2.04), and depressive symptoms (HR = 1.36) remained significant predictors. Interventions should be designed to minimize transition by managing smoking and depressive symptoms. Further research is required for associations between obesity and clinical progression to test the hypothesis of obesity paradox.

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In the United States and beyond, dementia cases are increasing in epidemic proportions. In 2017, it was estimated that approximately 50 million people have dementia worldwide, and 10 million new cases are expected to occur every year (World Health Organization [WHO], 2017). Alzheimer’s disease (AD) dementia is an irreversible, progressive neurodegenerative disorder that accounts for 60% to 80% of all dementias. In 2017, it was estimated that

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approximately 5.5 million Americans had AD dementia and, by 2050, an AD dementia diagnosis will occur every 33 seconds (Alzheimer's Association, 2017). However, curative treatments for AD dementia have not been established (Alzheimer's Association, 2017; WHO, 2017).

### **Mild cognitive impairment**

(MCI) is a prodromal stage of dementia, representing a transitional state between normal cognition and dementia. The etiologies and causes of MCI subtypes are different. Clinical subtypes of MCI include amnesic or non-amnesic (aMCI or non-aMCI). These profiles may be related to different patho-physiological processes. The aMCI subtype is characterized by a primary decline in memory function either alone (single-domain) or in conjunction with other cognitive domains (multiple-domain), but shows insufficient severity to constitute dementia. On the other hand, non-aMCI is diagnosed when individuals present impairments in non-memory cognitive domains (e.g., language, attention, executive function) (Petersen, 2004). The aMCI subtype would presumably represent a prodromal stage of AD dementia, whereas the non-aMCI subtype seems to progress to non-AD dementias, such as frontotemporal, Lewy body, or vascular dementia. The rate of progression to clinically diagnosable AD dementia was 10% to 15% per year among persons with aMCI; however, the rate was 1% to 2% per year among older adults with normal cognition (Petersen et al., 1999). Moreover, it has been reported that approximately 80% of aMCI can progress to AD dementia within 7 years (National Institute on Aging, 2017; Petersen et al., 1999).

Given that there is no current disease-modifying treatment for AD dementia, prevention is of major importance. Delaying onset by 5 years is estimated to reduce the number of American older adults with AD dementia by approximately one half by 2050 (Alzheimer's Association, 2015). Although the optimal time window for interventions to delay the onset of dementias is uncertain, administering preventive efforts during cognitively normal states (the preclinical phase) is likely to be more effective than starting when certain cognitive impairment (the prodromal phase: MCI) is already established (Karlavish et al., 2017; Winblad et al., 2016). Therefore, it is critical to understand risk factors for the onset of either aMCI or AD dementia to intervene where possible in the preclinical phase.

### **Subjective cognitive decline**

(SCD) refers to individuals' concerns about self-perceived cognitive decline compared to their previous cognitive abilities. However, persons with SCD are found to have clinically normal neuropsychological functions (Molinuevo et al., 2017), and although they are in the cognitively normal category, the presence of SCD may imply risk of future cognitive deterioration. A meta-analysis indicated that approximately 6.6% and 2.3% of older adults with SCD were diagnosed with MCI and dementia after 1 year, respectively, and having SCD doubled individuals' risk of developing dementia (Mitchell et al., 2014).

Previous studies have suggested that vascular and/or neuropsychiatric risk factors could affect the development of aMCI and AD dementia. Vascular risk factors include diabetes

mellitus (DM), hypercholesterolemia, hypertension, overweight/obesity, and cigarette smoking history. Anxiety and depressive symptoms were introduced as neuropsychiatric risk factors. Most of these risk factors are modifiable with the appropriate management or therapy. A meta-analysis of longitudinal studies indicated that individuals with type 2 DM had 50% higher risk of AD dementia than those without diabetes (Cheng et al., 2012). Observational studies indicated that type 2 DM, hypercholesterolemia, and hypertension multiply risk of aMCI or AD dementia by 1.1 to 2.4 times in older adults (Casado Naranjo et al., 2015; Li et al., 2011; Winkler et al., 2014). A meta-analysis of cohort studies showed that DM (adjusted combined odds ratio [COR] = 1.40), hypercholesterolemia (COR = 1.72), hypertension (COR = 1.31), and midlife obesity (COR = 1.88) were associated with increased risk of incident AD dementia later in life (Meng et al., 2014). It has also been suggested that increased body mass index (BMI) in midlife can be a risk factor of AD dementia. One-unit increases in midlife BMI corresponded with 6.7 months earlier onset of AD dementia (Chuang et al., 2016). In addition, compared to individuals with normal weight, being overweight or obese was associated with 70% higher risk of aMCI in individuals aged 60 years (Chuang et al., 2016; Wang et al., 2017).

Previous observational studies indicated that current smoking or cumulative cigarette exposure was associated with 1.7 to 3.4 times higher risk of aMCI or AD dementia compared to non-smoking in older adults (Aggarwal et al., 2006; de Bruijn et al., 2014; Xue et al., 2017). Individuals with anxiety are 1.3 to 1.8 times more likely to get AD dementia than those without anxiety in older adults aged >75 years (Mah et al., 2015; Palmer et al., 2007). In addition, individuals with depression had >50% higher risk of developing AD dementia compared to those without depression (Diniz et al., 2013). The presence of depression was also associated with 1.7 to 7.6 times higher risk of development of aMCI in individuals aged >70 years (Casado Naranjo et al., 2015; Geda et al., 2014; Sundermann et al., 2017).

Taken together, vascular and neuropsychiatric risk factors appear to be associated with the development of either aMCI or AD dementia. However, given that previous studies have rarely differentiated between SCD and non-SCD, there has been limited empirical consideration of the association between those risk factors and clinical progression (i.e., conversion to either aMCI or AD dementia) in persons with SCD. Therefore, the purpose of the current study was to identify modifiable risk factors contributing to the development of aMCI or AD dementia in individuals with SCD.

## METHOD

### Study Design and Population

The current study adopted a longitudinal cohort design. Data were drawn from the National Alzheimer's Coordinating Center's Uniform Data Set (NACC-UDS). Alzheimer's Disease Centers (ADCs) previously or currently funded by the National Institute on Aging (NIA) evaluate individuals approximately annually with the same standardized measures and provide data for research through the NACC, located at the University of Washington (Seattle, WA). As a result, the NACC-UDS has systematic de-identified information on characteristics of individuals. Because each ADC uses its own recruitment methods and

study protocols approved by its institutional review board (IRB), research using the NACC-UDS is not considered a population-based study (Beekly et al., 2007). The current study was not defined as human research, so it was exempt from IRB review and approval.

The presence of SCD was identified when individuals reported a decline in memory relative to previous abilities in a semi-structured interview with a trained clinician at their first visit (baseline). SCD was not subsequently assessed in the current study. The current study included individuals who were aged  $\geq 60$  years at baseline, given that the onset of SCD in adults older than 60 years is more closely linked to the Alzheimer's pathway (Jessen et al., 2014). Individuals with SCD were classified as cognitively normal based on the judgment of a trained clinician, having a Mini Mental State Examination (MMSE) score of  $\geq 27$ , and a Clinical Dementia Rating Dementia Staging Instrument (CDR) global score of 0 at baseline. The MMSE and CDR are standardized tools to comprehensively measure the presence and severity of cognitive impairment (Folstein et al., 1975; Hughes et al., 1982). The MMSE assesses seven cognitive domains: visual construction, language, recall, attention/calculation, registration, orientation to place, and orientation to time. Scores range from 0 to 30, with higher scores indicating better global cognition. The CDR assesses six cognitive domains: memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care. A global CDR rating indicates a certain cognitive status: 0 (*no impairment*), 0.5 (*questionable impairment*), 1 (*mild impairment*), 2 (*moderate impairment*), and 3 (*severe impairment*). The sample was further restricted to individuals who had follow-up evaluations. Individuals were not diagnosed with any type of MCI or dementia at baseline. The current analyses included 1,525 individuals from whom data had been collected between September 2005 and August 2018.

## Measures

As independent variables, vascular risk factors included DM, hypercholesterolemia, hypertension, overweight/obesity, and cigarette smoking history at baseline. Anxiety and depressive symptoms were assessed as neuropsychiatric risk factors at baseline. Information on DM, hypercholesterolemia, and hypertension was obtained from clinician assessment of medical history (yes/no). Medical history was determined based on self-report, informant-report, and medical records. Overweight/obesity was determined by BMI. The categorization of BMI followed the WHO criteria (weight in pounds  $\times 703$ )/(height in inches<sup>2</sup>): underweight ( $<18.5$  kg/m<sup>2</sup>), normal weight ( $\geq 18.5$  kg/m<sup>2</sup> and  $<25$  kg/m<sup>2</sup>), overweight ( $\geq 25$  kg/m<sup>2</sup> and  $<30$  kg/m<sup>2</sup>), and obese ( $\geq 30$  kg/m<sup>2</sup>). Individuals who reported they never smoked cigarettes during their lifetime were assigned to the non-smoker group and those who reported any history of cigarette smoking but did not smoke currently were designated as former smokers. If individuals reported they currently smoke, they were assigned to current smokers.

Anxiety or depressive symptoms were measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q), an informant-based report of symptoms that have occurred over the past 1 month. The NPI-Q is a structured interview with established reliability and validity (Kaufert et al., 2000). The presence of symptoms was reported as *no* (no symptoms reported) or *yes* (mild/moderate/severe symptoms). As a dependent variable, *clinical progression* was

defined as conversion to either aMCI or AD dementia during follow-up visits among individuals with SCD at baseline. For diagnosis of cognitive state, trained clinicians make determinations in accordance with published research diagnostic criteria. The diagnosis of aMCI included either single- or multiple-domain aMCI by the Petersen (2004) criteria. The confirmation of AD dementia was determined using either the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984) or the National Institute on Aging-Alzheimer's Association criteria (McKhann et al., 2011).

Baseline demographics, medical conditions that could affect cognition, and ADCs were included as covariates. Demographics included age (years), sex (male/female), education (years), race (White/Other), ethnicity (Hispanic/Other), and marital status (married/non-married [widowed, divorced, separated, or never married]). Medical conditions were measured by clinician assessment of individuals' medical history (yes/no), including Parkinson's disease, seizures, traumatic brain injury, stroke, vitamin B12 deficiency, alcohol or other substance use, atrial fibrillation, congestive heart failure, and thyroid disease. ADC was a categorical variable with de-identified numbers representing each of the 35 ADCs.

### Statistical Analysis

Descriptive statistics were means (standard deviations) and numbers (proportions), which were compared using analysis of variance (ANOVA) for continuous variables and chi-square tests or Fisher's exact tests for categorical variables for baseline characteristics by follow-up diagnosis between converters (i.e., conversion from SCD to either aMCI or AD dementia at follow-up visits) and non-converters. Univariate and multivariate Cox proportional hazard regression analyses were used to estimate hazard ratio (HR) with 95% confidence intervals (CI) of clinical progression with vascular and neuropsychiatric risk factors as primary predictors. Covariates controlled for confounders. Stepwise analyses were performed: univariate-unadjusted analyses in the first model. The second model adjusted for all covariates in univariate analyses. Independent variables were selected for further multivariate analyses if they revealed a significant *p* value in the second model. Multivariate analyses were performed in the third model adjusting mutually for selected independent variables and for all covariates. All analyses were conducted using IBM SPSS version 25.

## RESULTS

### Study Population Characteristics

Of 3,211 individuals, 1,686 were excluded based on age, MMSE score, CDR score, and number of evaluation criteria (i.e., no follow-up data). Thus, a total of 1,525 individuals with SCD were included in the current study (mean age = 73.8 [*SD* = 8.1, range = 60 to 99] years, mean education = 15.9 [*SD* = 2.8] years, 1,023 [67.1%] female, 81 [5.3%] Hispanic, 1,287 [84.4%] White, 840 [55.1%] married). The mean follow-up duration was 4.7 [*SD* = 2.9] years. At baseline, DM, hypercholesterolemia, and hypertension were present in 167 (11%), 789 (51.7%), and 775 (50.8%) individuals, respectively. Based on BMI, 595 (39%), 24 (1.6%), 569 (37.3%), and 337 (22.1%) were normal weight, underweight, overweight, and obese, respectively. Smoking history included no lifetime smoking (*n* = 772, 50.6%),

former smoking ( $n = 701$ , 46%), and current smoking ( $n = 52$ , 3.4%). Anxiety and depressive symptoms were present in 164 (10.8%; mild = 124, moderate = 35, severe = 5) and 239 (15.7%; mild = 179, moderate = 54, severe = 6) individuals, respectively.

There were 386 individuals who progressed to either aMCI ( $n = 335$ ) or AD dementia ( $n = 51$ ). Table 1 compares baseline characteristics between non-converters ( $n = 1,139$ ) and converters ( $n = 386$ ). Converters were older at baseline (mean age = 72.7 [ $SD = 7.8$ ] vs. 77 [ $SD = 8.3$ ] years,  $p < 0.001$ ), were less likely to be Hispanic (6% vs. 3.4%,  $p < 0.05$ ), married (56.5% vs. 50.8%,  $p < 0.05$ ), and abuse alcohol (4.6% vs. 2.1%,  $p < 0.05$ ). Converters also tended to be less obese (24.2% vs. 15.8%,  $p = 0.001$ ).

## Clinical Progression

**Hazard Models**—Table 2 shows Cox proportional hazard models for clinical progression (i.e., conversion to either aMCI or AD dementia). In the univariate-unadjusted model (Model 1), obese status was associated with less risk of clinical progression compared to normal weight status (HR = 0.59; 95% CI [0.44, 0.78]). In the univariate-adjusted model (Model 2), obese status (HR = 0.64; 95% CI [0.47, 0.88]), current smoking (HR = 2.02; 95% CI [1.18, 3.44], reference: no smoking), and depressive symptoms (HR = 1.35; 95% CI [1.03, 1.77]) were significant predictors of clinical progression after adjusting for all covariates (i.e., demographics, medical conditions, and indicators for ADCs). These significant independent variables were selected and entered into Model 3, which was adjusted mutually for selected predictors and for all covariates. As a result, the multivariate-adjusted Cox proportional hazard model demonstrated that obese status (HR = 0.64; 95% CI [0.47, 0.89]), current smoking (HR = 2.04; 95% CI [1.20, 3.50]), and depressive symptoms (HR = 1.36; 95% CI [1.03, 1.79]) remained significant predictors of clinical progression. Therefore, current smoking and depressive symptoms were risk factors of conversion; however, obese status was a protective factor of clinical progression in individuals with SCD.

## DISCUSSION

The goal of the current study was to identify risk factors associated with clinical progression in persons with SCD who underwent standardized clinical follow up with a mean duration of approximately 5 years. Leveraging a well-characterized national sample of cognitively normal older adults with SCD, obesity, current smoking, and depressive symptoms were found to be associated with clinical progression after adjusting for demographics and medical conditions that would affect cognition and ADC sites. Current smoking and depressive symptoms conferred an increased risk of clinical progression, but obesity was predictive of less clinical progression relative to normal weight. As few studies have investigated the prediction of clinical progression by modifiable risk factors in SCD, this study may present promising avenues for reducing risk of future cognitive impairment.

Findings are in line with previous studies that associate cigarette smoking with risk of clinical progression. Current smoking was predictive of AD dementia in older adults with an increased risk ranging from 1.7 to 3.4 times higher than no smoking (Aggarwal et al., 2006; Xue et al., 2017). Although the exact mechanisms by which smoking can exert its detrimental effects on MCI/dementia remain elusive, it has been hypothesized that risk may



markedly increase with greater cumulative cigarette exposure (Durazzo et al., 2014). A lifetime smoking habit was associated with a higher risk of aMCI (odds ratio [OR] = 2.45) and cerebral oxidative stress (effect size = 0.6) in older adults with normal cognition. Chronic cerebral oxidative stress was associated with at least 70% greater risk of AD dementia (de Bruijn et al., 2014; Durazzo et al., 2014; Durazzo et al., 2016). Further studies are necessary to elucidate mechanisms that would explain the association of smoking and clinical progression in individuals with SCD.

Findings related to depressive symptoms are also consistent with previous studies. Older adults with depressive symptoms (mean age = 79 years) had an increased risk of AD dementia (HR = 1.76) in the Framingham Heart Study (Saczynski et al., 2010). Depressive symptoms were also proposed as a risk factor for the incidence of aMCI with HR ranging from 1.74 to 2.22 in community-dwelling older adults aged >70 years (Geda et al., 2014; Sundermann et al., 2017). Given that 75% (179/239) of symptoms were mild in the current study, managing even minor depressive symptoms may be important to delay objective cognitive decline in SCD.

Obesity acted as a protective factor of clinical progression in the current study. Generally, individuals who experience weight gain may be at risk of the presence of AD dementia and/or AD neuropathology due to deleterious effects of increased adiposity. Previous studies indicated that midlife obesity is predictive of AD dementia in later life and 1-unit increases in midlife BMI affected earlier onset of AD dementia by 6.7 months (Chuang et al., 2016; Meng et al., 2014). However, the relationship between BMI and risk of onset of MCI or AD dementia becomes equivocal with increasing age. A meta-analysis showed that being obese at age <65 years has a positive association with incident dementia (risk ratio = 1.41), but being obese at age >65 years has a negative association with incident dementia (risk ratio = 0.83) (Peditzi et al., 2016).

There are a few reasons that could explain this “obesity paradox” in older adults. First, the AD-related neurodegenerative brain changes may increase energy expenditure, which may obscure the relationship between later life obesity and risk of AD dementia. Second, weight loss is primarily due to sarcopenia and not a loss of fat in older adults. Therefore, total body weight and BMI may not be valid surrogate measures of fat accumulation in older adults (Alhurani et al., 2016; Müller et al., 2017; Peditzi et al., 2016). Other body composition metrics are likely to be more accurate measures of adiposity for older adults. For example, using the waist-to-hip ratio as a measure of central obesity reveals that abdominal obesity was associated with the development of AD dementia (HR = 2.5), whereas BMI in the same older cohort was not predictive of AD dementia. In addition, central obesity showed a significant association with aMCI (OR = 1.73) in community-dwelling older adults with a mean age of 66 years who did not report SCD (Feng et al., 2013; Luchsinger et al., 2012). Future research for older adults with SCD needs to use a measure of abdominal fat given that central obesity may be a more reliable vascular risk factor to predict clinical progression than global obesity as measured with BMI.

Lack of significant findings for other vascular risk factors in the current study may result from chronicity, which could not be exactly measured in the dataset. A meta-analysis of

cohort studies for midlife vascular risk factors indicated that hypertension (COR = 1.31), hypercholesterolemia (COR = 1.72), and DM (COR = 1.40) in midlife were associated with higher risk of incident AD dementia in later life (Meng et al., 2014). Some time lag may exist between exposure to these risk factors and clinical progression. Meanwhile, baseline anxiety was not predictive of aMCI but predicted non-aMCI (HR = 2.74), whereas depression predicted aMCI (HR = 1.74) but not non-aMCI in older adults with a median age of 79 years (Geda et al., 2014). Anxiety and depressive symptoms may affect clinical progression differently; however, further studies are necessary to draw conclusions.

## LIMITATIONS

Although the standardized NACC-UDS data are reliable, findings of the current study should be interpreted cautiously as the sample from the NACC database contained a disproportionate representation of female gender, White race, and high educational attainment compared to the general population. Thus, the findings from this study may reflect sample characteristics specific to the NACC cohort. Additional studies are required to determine the extent to which the results of this study may be generalized to population-based samples with SCD. In addition, although the statistical models contained a variety of covariates that would be related to cognition, the covariates were not all-inclusive. For example, the study did not include the use of anticholinergics as well as lifestyle levels, such as physical activity and diet patterns, as covariates that may affect cognition due to availability.

## IMPLICATIONS

### Clinical

Our findings have several clinical implications. First, health care providers (e.g., clinicians, nurses) need to invite older adults to discuss the presence of SCD and assess SCD early. According to the Centers for Disease Control and Prevention, in 2018, only 45.3% of persons with SCD aged 45 years discussed their symptoms (i.e., SCD) with a health care provider (48.8% in persons aged 45 to 64 years and 39.8% in persons age 65 years). To assess the number of individuals with SCD accurately, health care providers should encourage older adults to discuss any cognitive concerns at medical appointments. Second, health care providers need to educate older adults with SCD about manageable risk factors. Health care providers can also increase awareness of the importance of managing cigarette smoking and depressive symptoms for older adults with SCD as initial care plans. Third, for older adults with SCD, in the context of current smoking and/or depressive symptoms, health care providers may consider appropriate interventions, such as a smoking cessation program and cognitive-behavioral therapy to manage risk factors. Last, the impact of interventions should be evaluated at routine follow ups by seeing whether the programs would delay the progression to aMCI or AD dementia among older adults with SCD.

### Research

The current study findings have several implications for future research. SCD was measured at only one time point to select the study sample. It is possible that the trajectory of SCD



may be an important indicator for later conversion to aMCI or AD dementia. For example, older adults with persistent SCD over time may be more susceptible to conversion to aMCI/AD dementia than those who only reported SCD one time. Future research is also needed to examine if modifiable vascular and/or neuropsychiatric risk factors are differently associated with clinical progression between individuals with persistent and intermittent SCD during the specific time frame. Furthermore, the combined effects of modifiable vascular and/or neuropsychiatric risk factors and SCD on clinical progression need to be studied, particularly in comparison to a cohort without SCD at baseline.

## CONCLUSION

The results of the current study demonstrate that current cigarette smoking and depressive symptoms were predictive of clinical progression, as opposed to obesity, which was associated with a reduced risk of conversion to either aMCI or AD dementia in individuals with SCD. These results underscore the need for further research to elucidate associations between obesity and clinical progression using other body composition metrics than BMI in older adults with SCD.

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**TABLE 1**

Baseline Characteristics of Study Population by Follow-Up Status (*N* = 1,525)

Characteristic	<i>n</i> (%)		<i>p</i> Value
	Non-Converters ( <i>n</i> = 1,139)	Converters ( <i>n</i> = 386)	
Female	762 (66.9)	261 (67.6)	0.796
White	954 (83.8)	333 (86.3)	0.240
Hispanic	68 (6)	13 (3.4)	0.049*
Married	644 (56.5)	196 (50.8)	0.049*
Parkinson's disease	18 (1.6)	2 (0.5)	0.113
Seizures	24 (2.1)	7 (1.8)	0.724
Traumatic brain injury	130 (11.4)	32 (8.3)	0.085
Stroke	31 (2.7)	18 (4.7)	0.062
Vitamin B12 deficiency	55 (4.8)	21 (5.4)	0.633
Alcohol use	52 (4.6)	8 (2.1)	0.029*
Substance use <sup>a</sup>	18 (1.6)	1 (0.3)	0.059
Atrial fibrillation	81 (7.1)	29 (7.5)	0.792
Congestive heart failure	29 (2.5)	6 (1.6)	0.261
Thyroid disease	239 (21)	92 (23.8)	0.240
Diabetes	124 (10.9)	43 (11.1)	0.891
Hypercholesterolemia	600 (52.7)	189 (49)	0.207
Hypertension	578 (50.7)	197 (51)	0.922
Body mass index			0.001**
Normal	425 (37.3)	170 (44)	
Underweight	14 (1.2)	10 (2.6)	
Overweight	424 (37.2)	145 (37.6)	
Obese	276 (24.2)	61 (15.8)	
Smoking history			0.501
No smoking	572 (50.2)	200 (51.8)	
Former smoking	531 (46.6)	170 (44)	

Characteristic	n (%)		p Value
	Non-Converters (n = 1,139)	Converters (n = 386)	
Current smoking	36 (3.2)	16 (4.1)	
Anxiety	121 (10.6)	43 (11.1)	0.777
Depressive symptoms	170 (14.9)	69 (17.9)	0.168
	Mean (SD) (Range)		
Age (years)	72.7 (7.8) (60 to 99)	77 (8.3) (60 to 99)	<0.001 ***
Education (years)	15.9 (2.8) (2 to 24)	15.8 (2.9) (4 to 23)	0.468

Note. Converters are individuals who progressed from subjective cognitive decline to either amnesic mild cognitive impairment or Alzheimer's dementia.

<sup>a</sup>Fisher's exact test.

\* p < 0.05;

\*\* p < 0.01;

\*\*\* p < 0.001.



**TABLE 2**

Cox Proportional Hazard Models for Clinical Progression (N = 1,525)

Characteristic	Model 1		Model 2		Model 3	
	HR (CI)	p Value	HR (CI)	p Value	HR (CI)	p Value
Diabetes	1.08 [0.79, 1.48]	0.634	1.08 [0.77, 1.52]	0.656	–	–
Hypercholesterolemia	0.98 [0.80, 1.20]	0.828	1.02 [0.83, 1.26]	0.843	–	–
Hypertension	1.12 [0.91, 1.36]	0.285	0.93 [0.75, 1.15]	0.476	–	–
Body mass index						
Underweight	1.46 [0.77, 2.76]	0.247	1.46 [0.75, 2.83]	0.263	1.34 [0.69, 2.62]	0.393
Overweight	0.82 [0.66, 1.02]	0.076	0.94 [0.74, 1.18]	0.592	0.95 [0.76, 1.20]	0.684
Obese	0.59 [0.44, 0.78]	<0.001***	0.64 [0.47, 0.88]	0.006***	0.64 [0.47, 0.89]	0.007***
Smoking history						
Former smoking	0.97 [0.79, 1.19]	0.755	0.94 [0.76, 1.17]	0.591	0.95 [0.77, 1.18]	0.631
Current smoking	1.49 [0.89, 2.48]	0.127	2.02 [1.18, 3.44]	0.010*	2.04 [1.20, 3.50]	0.009***
Anxiety	1.11 [0.81, 1.52]	0.529	1.15 [0.82, 1.61]	0.409	–	–
Depressive symptoms	1.22 [0.94, 1.59]	0.129	1.35 [1.03, 1.77]	0.033*	1.36 [1.03, 1.79]	0.028*

Note. HR = hazard ratio; CI = 95% confidence interval. Model 1: HR was not adjusted; Model 2: HR was adjusted for all covariates; Model 3: HR was adjusted for all covariates and for other included independent variables. Clinical progression was defined as conversion to either amnesic mild cognitive impairment or Alzheimer's dementia. Covariates include baseline age, sex, education, race, ethnicity, marital status, Parkinson's disease, seizures, traumatic brain injury, stroke, vitamin B12 deficiency, alcohol or other substance use, atrial fibrillation, congestive heart failure, thyroid disease, and indicators for Alzheimer's Disease Center site.

\* p < 0.05;

\*\* p < 0.01;

\*\*\* p < 0.001.