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LOW HEMOGLOBIN A1C INCREASES THE RISK OF DISABILITY IN COMMUNITY-DWELLING OLDER NON-DIABETICS ADULTS

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Abstract: *Objective:* To describe the health characteristics of individuals with low HbA1c levels and evaluate the association between HbA1c level and disability or all-cause mortality in non-diabetic older adults. *Design:* Prospective observational cohort study. *Setting:* Seongnam, Gyeongi Province, Korea. *Participants:* Among the 1,000 community-dwelling Koreans ≥ 65 years of age who were followed for 5 years, 760 non-diabetic individuals were analyzed. *Measurements:* Activities of Daily Living (ADL) and Instrumental ADL (IADL) were evaluated and mortality data were obtained from the National Statistics Office of Korea. *Results:* The mean age was 76.3 (SD 9.0) years, and 319 subjects (42.0%) were male. Lower level of HbA1c was associated with less frequent hypertension and less frequent use of aspirin or statin, and lower values of body mass index, hematocrit, total iron-binding capacity, albumin, and cholesterol level. The participants were categorized into 3 groups according to their HbA1c (group I, < 5.5%; group II, 5.5~5.9%; and group III, 6.0 ~ 6.4%). Although, there was no significant difference in functional status according to baseline HbA1c level, disability was more frequently observed as the HbA1c level decrease (18.3% in group I, 12.5% in group II, and 5.3% in group III, p=0.029) at the 5-year follow-up evaluation. There were 172 deaths (22.6%) during the follow-up period. There was no significant difference in mortality among the groups, however, group I had a 2.071-fold higher risk for the incident disability or mortality over group III after adjusting age, gender, and possible confounder (95% CI: 1.040 ~ 4.124, p=0.038). *Conclusions:* Lower level of HbA1c was associated with an increased risk of disability in non-diabetic older adults.

Key words: Cohort study, disability, elderly, hemoglobin A.

Introduction

Hemoglobin A1c (HbA1c) is the standard measure of glucose control and is now recommended for use as a diagnostic test for diabetes. A number of studies have shown that HbA1c values, even below the diagnostic threshold of 6.5%, are associated with clinical outcomes including cardiovascular events, kidney disease, and total mortality (1-3).

Interestingly, previous studies have reported a J-shaped association between HbA1c level and all-cause mortality in non-diabetic populations (1, 4, 5). Very low HbA1c values among individuals without diabetes may reflect underlying biological processes, such as red blood cell (RBC) abnormality, inflammation, malnutrition, or liver dysfunction. However, little is known about the biological factors associated with increased mortality in non-diabetic individual.

Physical disability is a major adverse health outcome associated with aging and is an independent risk factor for the mortality, impaired quality of life, and further functional decline in older adults (6-8). Accordingly, identifying risk factors for disability in older adults has been one of the main topics in a gerontology research field.

Diabetes has been reported to be a risk factor for disability in older adults (9). The higher prevalence of functional disability in older diabetic patients might be a result of diabetes-related complications. However, it has not been evaluated whether HbA1c levels are related with functional status in older individual without diabetes.

The purpose of the present study is to describe the health characteristics of individuals with low HbA1c levels and evaluate the association between HbA1c level and disability or all-cause mortality in non-diabetic older adults.

This question is worth addressing because identifying the association between HbA1c level and disability may be helpful in elucidating precise mechanisms related to disability and may thus be used to develop new therapeutic targets to improve the functional status of older adults.

Methods

Study Population, Subject Evaluation, and Laboratory Study

This study was conducted as a part of the Korean Longitudinal Study on Health and Aging (KLoSHA), which includes a randomly selected, community-based, elderly population (10, 11). (Supplementary figure 1).

After obtaining written informed consent, all participants completed a standardized clinical interview consisting of physical and neurological examinations by 3 clinicians. Additional interviews using standardized questionnaires were carried out by 3 nurses. The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital (SNUBH) in 2005 and 2010. This study was

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performed according to the Declaration of Helsinki.

Blood samples were obtained in the morning after at least 10 hours overnight fasting. The fasting plasma concentration of glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured using the Toshiba 200FR NEO chemistry analyzer (Toshiba Medical Systems Co., Tokyo, Japan). HbA1c was measured with a Bio-Rad variant II Turbo HPLC analyzer (Bio-Rad Laboratories, Inc., Hercules, CA, USA) in the National Glycohemoglobin Standardization Program (NGSP) level I certified laboratory at SNUBH.

Body weight and height were measured for subjects wearing light clothing without shoes. The glomerular filtration ratio (GFR) was calculated using the CKD-epidemiology collaboration (CKD-EPI) equation.

Definitions

Participants were considered hypertensive if they had blood pressure ≥ 140/90 mmHg or were taking antihypertensive medications. Participants were considered to have diabetes mellitus if they were receiving insulin or oral hypoglycemic medications or if their fasting blood glucose levels exceeded 126 mg/dL or HbA1c levels exceeded 6.5%. Alcohol consumption was defined as 12 or more standard drinks during the previous 12 months. One standard drink contains approximately 15 g of ethanol (12). Regular exercise was defined as > 30 minutes of moderate or vigorous physical activity at least three times a week.

Assessment of Disability

The functional status was measured by the 7 domains contained in the Activities of Daily Living (ADL; dressing, washing hands and face, bathing, toileting, eating, ambulating in and out of bed, and maintaining control of bowel and/or bladder functions) and by the 10 domains contained in the Instrumental Activities of Daily Living (IADL; decorating, housework, preparing meals, laundry, outgoing for a short distance, using transportation, shopping, handling money, using the telephone, and taking medicine). For each item, respondents were asked if they were able to perform the activities "without any assistance from another person (scored 1)," "with the assistance of another person (scored 2)," or "with absolute dependence on another person (scored 3)." Thus, ADL score ranged from 7 to 21 and IADL score ranged from 10 to 30, higher scores representing more dependency. We calculated the mean score of ADL and IADL by dividing the sum of the scores in all domains by the total number of domains. ADLs and IADLs were measured using the Korean ADL and IADL scale (13), which has been validated as a reliable tool for quantifying elderly function.

Functional Outcomes and Mortality

We defined disability as answering at least 1 domain with absolute dependence in either the ADL or IADL. We also defined the progression of disability as an increased number of domains answered "with absolute dependence" during a follow-up examination (14). A decrease of 2 points or more from baseline on total ADL or IADL was defined as functional decline (15).

All participants were flagged for mortality at the National Statistical Office of Korea, which provided the date and cause of all deaths occurring until the end of December 2011. We added the mortality data from Statistics Korea to our dataset using each individual's unique identifier.

Statistical Analysis

All statistical analyses were performed using SPSS (version 20.0, Armonk, NY: IBM Corp, USA). Continuous variables are expressed as the mean (SD) and were compared by either the unpaired Student's t-test or an analysis of variance (ANOVA) followed by a post-hoc comparison with the Scheffe test. Discrete variables are expressed as counts and percentages, and the $\chi 2$ or Fisher's exact test was used to compare proportions. Pearson's correlation coefficients were calculated between HbA1c and other variables.

Repeated-measures ANOVA or the paired t-test was used to assess changes that occurred over time within the HbA1c group. Multivariable analyses were adjusted for age, gender, and other potential confounding factors, such as hypertension, body mass index (BMI), white blood cell (WBC) counts, hemoglobin, iron, total iron-binding capacity (TIBC), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), albumin, GFR, and aspirin or statin treatment. All statistical tests were two-tailed, and P-values < 0.05 were considered to be statistically significant.

Results

Baseline characteristics of the participants according to HbA1c level

The mean age was 76.3 (SD 9.0) years, and 319 subjects (42.0%) were male. The duration of the follow-up period was 62.9 ± 16.9 months. HbA1c levels were related to the levels of WBC counts (r=0.110, P=0.002), hematocrit (r=0.101, P=0.005), TIBC (r=0.141, P < 0.001), transferrin (r=0.206, P < 0.001), ESR (r=0.140, P < 0.001), total cholesterol (r=0.118, P=0.001), protein (r=0.159, P < 0.001) as well as albumin (r=0.147, P < 0.001) concentration.

The participants were categorized into 3 groups according to their HbA1c (group I, < 5.5%; group II, 5.5~5.9%; and group III, 6.0 ~ 6.4%) (Table 1). Participants with a lower HbA1c had lower BMI, lower prevalence of hypertension, less frequent treatment with aspirin or statin, and lower level of protein, albumin, ESR, WBC count, hematocrit, TIBC and ALT.

However, there was no significant difference in the prevalence of disability according to the HbA1c group. Furthermore, mean scores of ADL and IADL were not significantly different among the three HbA1c group.

Table 1
Baseline characteristics of the study participants

	Total	Hemoglobin A1C (HbA1c)			
		< 5.5%	5.5 ~ 5.9%	6.0 ~ 6.4%	p-value
Number	760	174	404	182	
Age (years)	76.3 ± 9.0	75.8 ± 8.9	76.8 ± 9.1	75.8 ± 8.8	0.285
Male sex, n (%)	319 (42.1%)	79 (45.4%)	172 (42.6%)	68 (37.4%)	0.288
BMI (kg/m^2)	23.5 ± 3.2	22.9 ± 3.2	23.3 ± 3.1	24.8 ± 3.3	<0.001
Living alone, n (%)	118 (15.9%)	25 (14.7%)	65 (16.5%)	28 (15.7%)	0.754
Occupation (presence), n (%)	89 (11.8%)	21 (12.1%)	48 (12.0%)	20 (11.2%)	0.958
Current smoker, n (%)	89 (11.8%)	17 (9.8%)	57 (14.2%)	15 (8.3%)	0.068
Alcohol drinking, n (%)	167 (22.1%)	44 (25.4%)	95 (23.8%)	28 (15.5%)	0.151
Regular exercise, n (%)	362 (48.1%)	81 (46.6%)	188 (47.1%)	93 (52.0%)	0.500
Hx of cancer, n (%)	54 (7.1%)	14 (8.0%)	27 (6.7%)	13 (7.1%)	0.843
Hx of stroke/TIA, n (%)	78 (10.3%)	23 (13.2%)	34 (8.4%)	21 (11.5%)	0.177
Hypertension, n (%)	527 (69.7%)	114 (65.5%)	269 (67.1%)	144 (79.6%)	0.004
ACEi or ARB, n (%)	82 (10.8%)	16 (9.2%)	44 (10.9%)	22 (12.1%)	0.676
CCB, n (%)	136 (17.9%)	31 (17.8%)	67 (16.6%)	38 (20.9%)	0.455
Aspirin, n (%)	106 (14.2%)	15 (8.8%)	52 (13.1%)	39 (21.5%)	0.002
Statin, n (%)	55 (7.2%)	6 (3.4%)	29 (7.2%)	20 (11.0%)	0.023
SBP (mmHg)	131.1 ± 17.7	131.8 ± 17.6	130.7 ± 18.7	131.4 ± 15.3	0.782
DBP (mmHg)	82.5 ± 10.7	83.7 ± 11.5	82.0 ± 10.7	82.3 ± 10.0	0.198
ADL disability, n (%)	38 (5.0%)	8 (4.6%)	26 (6.5%)	4 (2.2%)	0.091
IADL disability, n (%)	150 (19.8%)	33 (19.0%)	89 (22.2%)	28 (15.5%)	0.161
WBC (x 10^3/μL)	6.1 ± 1.7	5.9 ± 1.7	6.1 ± 1.8	6.4 ± 1.5	0.008
Hemoglobin (g/dL)	13.6 ± 1.5	13.5 ± 1.6	13.5 ± 1.4	13.8 ± 1.4	0.067
Hematocrit (%)	41.5 ± 4.1	41.2 ± 4.8	41.3 ± 3.8	42.2 ± 4.0	0.015
RDW (%)	13.2 ± 1.1	13.3 ± 1.7	13.2 ± 0.9	13.2 ± 0.8	0.822
Iron (μg/dL)	98.9 ± 35.8	104.7 ± 41.9	97.8 ± 35.4	95.6 ± 29.2	0.041
TIBC (μg/dL)	320.2 ± 52.3	310.1 ± 50.4	318.8 ± 53.2	332.9 ± 50.0	<0.001
Ferritin (ng/mL)	112.6 ± 115.2	123.1 ± 146.2	115.9 ± 117.8	95.2 ± 62.5	0.054
ESR (mm/hr)	20.5 ± 14.4	17.0 ± 12.7	21.1 ± 15.1	22.6 ± 13.8	<0.001
Cholesterol (mg/dL)	204.2 ± 37.6	199.1 ± 36.5	204.2 ± 37.8	208.8 ± 37.6	0.052
Glucose (mg/dL)	99.3 ± 10.1	95.7 ± 8.7	98.5 ± 9.9	104.6 ± 9.9	<0.001
Protein (g/dL)	7.4 ± 0.5	7.3 ± 0.5	7.4 ± 0.5	7.6 ± 0.4	<0.001
Albumin (g/dL)	4.1 ± 0.3	4.0 ± 0.3	4.1 ± 0.2	4.1 ± 0.2	0.002
ALT (U/L)	19.9 ± 11.3	20.0 ± 10.9	19.1 ± 11.4	21.8 ± 11.5	0.026
AST (U/L)	24.9 ± 11.2	25.5 ± 9.8	24.5 ± 12.9	25.1 ± 7.9	0.610
BUN (mg/dL)	16.6 ± 5.3	16.4 ± 5.4	16.6 ± 5.3	16.9 ± 5.2	0.707
Creatinine (mg/dL)	0.91 ± 0.32	0.93 ± 0.45	0.90 ± 0.27	0.92 ± 0.26	0.565
GFR (ml/min/1.73 m^2)	72.4 ± 16.8	73.2 ± 17.4	72.6 ± 16.5	71.3 ± 16.9	0.560
hsCRP (mg/dL)	0.24 ± 0.65	0.19 ± 0.54	0.25 ± 0.74	0.25 ± 0.54	0.503

BMI; body mass index, Hx; history, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, CCB; calcium channel blocker, SBP; systolic blood pressure, DBP; diastolic blood pressure, ADL; activity of daily living, IADL; instrumental activity of daily living, WBC; white blood cell, RDW; red cell distribution width, TIBC; total iron-binding capacity, ESR; erythrocyte sedimentation rate, ALT; alanine transaminase, AST; aspartate transaminase, BUN; blood urea nitrogen, GFR; glomerular filtration rate, hsCRP; high-sensitivity C-reactive protein

Impact of HbA1c level on ADL or IADL changes

Among the 370 participants who had performed the 5-year follow-up functional evaluation, 44 (11.9%) showed ADL or IADL disability and 162 (43.8%) participants developed functional decline. The prevalence of disability, progression of disability, or functional decline was higher in the lower HbA1c group (Figure 1). In addition, mean scores of IADL were increased at the follow-up evaluation, but there was a significant interaction between IADL score changes and HbA1c group (P=0.049) by the repeated-measures ANOVA analysis (Figure 2, Supplementary figure 2).

Figure 1

Prevalence of functional decline, progression of disability, and disability at the follow-up evaluation according to HbA1c group

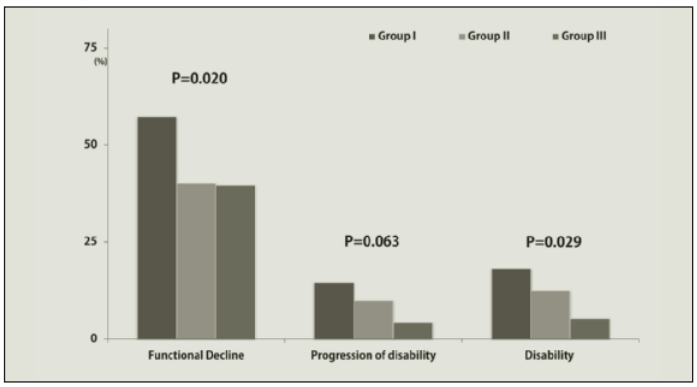
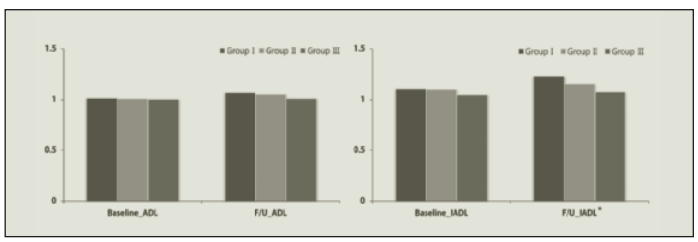


Figure 2

Changes of mean ADL or IADL scores according to HbA1c group



Mean ADL or IADL scores (dividing the sum of the ADL or IADL scores in all domains by the total number of domains, higher value indicating more functional impairment) were compared among three groups using one-way analysis of variance. ADL, activity of daily living; IADL, instrumental activity of daily living; *; P=0.044 by ANOVA.

Level of HbA1c in the prediction of incident disability or all-cause mortality

Among the 760 participants, 172 (22.6%) died before the end of December 2011 (168 subjects died before the follow-up examination, and 4 subjects died after the follow-up examination). There was no significant difference in mortality among the groups. However, baseline HbA1c level was higher in participants who maintained functional status compared with participants who died or had disability at follow-up examination (5.71 ± 0.36% vs. 5.64 ± 0.33%, p=0.017). In addition, the incidence of disability was significantly higher in participants who showed decrease in HbA1c level at the follow-up examination compared with baseline examination (16.7%, 5.9%, and 6.9% in participants who showed decrease, no change, and increase in HbA1c value at the follow-up examination respectively, p=0.021). Furthermore, group I had a 2.071-fold higher risk for the incident disability or mortality over group III after adjusting age, gender, and possible confounder (95% CI: 1.040 ~ 4.124, p=0.038) (Table 2).

Discussion

In this study, we showed that HbA1c level was inversely associated with increased risk of functional decline or disability in non-diabetic community-dwelling older Korean adults. Moreover, after adjusting possible confounding factors such as nutritional status, RBC abnormality, and general health condition, the association between HbA1c level and disability was maintained, which suggest possible independent underlying mechanism linking those two conditions.

Several reports have been published to show the inverse relationship between HbA1c level and all-cause mortality in non-diabetic populations, however, there were no previous reports to show the impact of HbA1c level on the functional status in older population, which is contrast to the established influence of HbA1c level on functional decline in diabetic patients.

The prevalence of disability increase with aging, and chronic diseases are associated with the development of disability in older adults. Accordingly, the identification of chronic diseases or conditions, which have clinical impacts on the functional status of older adults, is important for the prevention of general health status of older adults.

In this study, we showed that the levels of HbA1c as well as the changes of HbA1c levels were associated with functional decline or disability in community-dwelling older adults. The etiology of these relationships is largely unclear but may reflect some disease processes affecting HbA1c values. HbA1c values are largely dependent on the circulating glucose levels, however, it is possible that non-glycemic factors may be of disproportionate importance in the low range of HbA1c. Accordingly, the relationship between levels of HbA1c and disability might be mediated with the underlying diseases, not by the independent association.

Previous report showed a consistent increase in HbA1c with age in non-diabetic populations (16). Accordingly, the influence of HbA1c on disability might not be associated with aging effect. Moreover, the risk of incident disability was higher in participants who showed decrease in HbA1c levels at the follow-up examination. In contrast, these processes can be influenced by factors such as RBC life span, iron handling, and glucose distribution across the erythrocyte membrane and perhaps as-yet undiscovered mechanisms. It has been reported that RBC survival varies sufficiently among hematologically normal people to cause clinically important differences in

Table 2
Unadjusted and adjusted odds ratio for the risk of incident disability or mortality

	Unadjusted OR (95% CI)	Age, gender adjusted OR (95% CI)	Fully adjusted† OR (95% CI)
HbA1c group			
Group II (over group III)	1.368 (0.909 ~ 2.061)	1.249 (0.779 ~ 2.002)	1.185 (0.663 ~ 2.117)
Group I (over group III)	1.764 (1.104 ~ 2.819)	2.064 (1.195 ~ 3.567)	2.071 (1.040 ~ 4.124)

†Adjusted for age, gender, body mass index, hypertension, white blood cell count, hemoglobim, albumin, alanine transaminase, erythrocyte sedimentation rate, glomerular filtration rate, iron, total iron-binding capacity, aspirin treatment, and statin treatment

HbA1c (17). In addition, HbA1c values were affected by iron storage status, hemoglobin level, RBC abnormality, gender, and ethnicity (18). Especially, RBC abnormality has been known to be associated with an extremely low level of HbA1c. Accordingly, certain health conditions that decrease erythrocyte life span are known to alter HbA1c values. In the present study, hematocrit levels was significantly lower in participants with lower HbA1c level, however, iron storage markers, such as iron, TIBC, and ferritin level, were not decreased in participants with lower HbA1c level. Accordingly, abnormalities in RBC dynamics or iron storage may not be the main factors linking the relationship between HbA1c level and disability in our results.

In the present study, participants with low HbA1c values had unfavorable profiles of nutritional factors such as low protein, low albumin, and low BMI levels. Accordingly, it is possible that low level of HbA1c may be associated with lower glucose level or hypoglycemia. It has been well known that hypoglycemia among treated diabetic older adults is a risk factor of cognitive decline, disability, and mortality (19, 20). However, it is not clear whether hypoglycemia is also significant risk factor in non-diabetic, non-treated participants. Nonetheless, previous reports showed that hypoglycemic episodes occur even among non-diabetic hospitalized older patients and the increased mortality is not associated drug-treatment but linked with comorbidities (21, 22). Accordingly, there remained possibility that the association between low HbA1c level and increased risk of disability may be related with the risk of hypoglycemia or other nutritional factors (23).

Our study had several potential limitations to be considered in the interpretation of these results. Although, we examined the possible confounding effect of other variables with the association between HbA1c and disability, however, there remained possibility that unmeasured factors may be remained the inter-relationship. In addition, we attempted to follow the participants for 5 years, but 30.5% of the initial sample could not be interviewed during a second examination. There were substantial differences in baseline characteristics among the subjects who completed the follow-up evaluation, did not complete follow-up evaluation, and died during the follow-up period (Supplementary table). The observed inferiority in the follow-up loss groups could lead to inevitable selection bias which may be considered to be a limitation of the study. However, there was no significant difference in the lost to follow-up rate among the 3 different HbA1c groups (Supplementary figure 1). Thus, we believe that the high drop-out rate may not have significant impact on the association between HbA1 level and incident disability in this analysis.

Still, we are the first to notice that lower level of HbA1c was associated with an increased risk of disability in non-diabetic older adults. This association remained significant even after adjustments for demographic, socio-economic, and clinical factors. Accordingly, identifying the possible mechanism linking those two conditions should be encouraged.

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Conflict of interest: : There is no conflict of interest among all authors.

Ethical standards: The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital (SNUBH) and was performed according to the Declaration of Helsinki.

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Figure 1 Supplementary

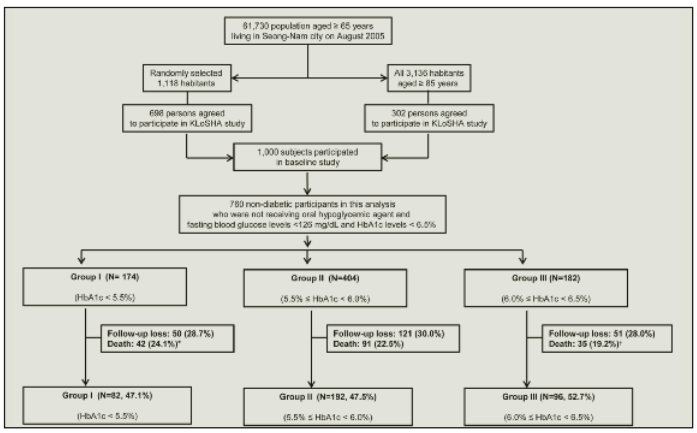

Figure 2 Supplementary

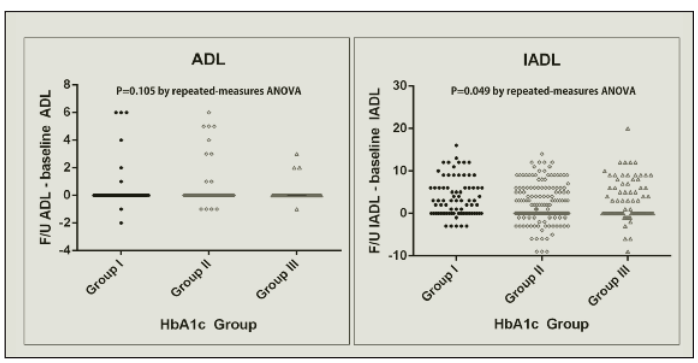

Table 1 Supplementary

	Follow-up (N=370)	Follow-up Loss (N=222)	Dead (N=168)	P value*
Age (years)	72.6 ± 7.3	76.5 ± 8.7	84.3 ± 7.4	<0.001
Male sex, n (%)	171 (46.2%)	73 (32.9%)	75 (44.6%)	0.005
BMI (kg/m^2)	23.8 ± 3.2	23.7 ± 3.3	22.3 ± 2.9	<0.001
Living alone, n (%)	52 (14.2%)	43 (19.7%)	23 (14.5%)	<0.001
Occupation (presence), n (%)	60 (16.3%)	17 (7.8%)	12 (7.3%)	0.001
Current smoker, n (%)	40 (10.8%)	22 (9.9%)	27 (16.4%)	0.176
Alcohol drinking, n (%)	101 (27.4%)	34 (15.3%)	32 (19.5%)	0.003
Regular exercise, n (%)	207 (56.4%)	110 (49.8%)	45 (27.4%)	<0.001
Hypertension, n (%)	256 (69.2%)	154 (69.4%)	117 (71.3%)	0.875
CVA, n (%)	29 (24.2%)	31 (37.3%)	18 (29.5%)	0.385
Cancer, n (%)	29 (7.9%)	16 (7.3%)	9 (5.5%)	0.623
SBP (mmHg)	132.0 ± 16.8	130.7 ± 18.8	129.8 ± 18.1	0.361
DBP (mmHg)	83.2 ± 10.4	82.4 ± 10.8	80.9 ± 11.2	0.073
ADL disability, n (%)	3 (0.8%)	10 (4.5%)	25 (15.1%)	<0.001
IADL disability, n (%)	26 (7.0%)	43 (19.4%)	81 (49.1%)	<0.001
WBC (x 10^3/μL)	6.2 ± 1.7	6.2 ± 1.8	6.1 ± 1.6	0.706
Hemoglobin (g/dL)	13.9 ± 1.5	13.5 ± 1.3	13.1 ± 1.5	<0.001
Hematocrit (%)	42.2 ± 4.1	41.3 ± 3.7	40.1 ± 4.2	<0.001
RDW (%)	13.1 ± 1.3	13.1 ± 0.8	13.5 ± 1.0	<0.001
Iron (μg/dL)	105.3 ± 36.9	98.7 ± 33.8	84.9 ± 31.7	<0.001
TIBC (μg/dL)	321.7 ± 49.0	324.1 ± 50.5	311.6 ± 60.5	0.051
Ferritin (ng/mL)	111.1 ± 5.7	109.5 ± 9.1	120.0 ± 7.9	0.641
ESR (mm/hr)	18.0 ± 11.5	20.7 ± 14.0	25.9 ± 18.5	<0.001
Cholesterol (mg/dL)	203.9 ± 37.9	209.0 ± 37.4	198.4 ± 36.3	0.023
Glucose (mg/dL)	100.2 ± 10.2	99.7 ± 9.7	96.8 ± 10.3	0.001
Protein (g/dL)	7.5 ± 0.4	7.4 ± 0.5	7.3 ± 0.5	<0.001
Albumin (g/dL)	4.1 ± 0.2	4.1 ± 0.3	4.0 ± 0.3	<0.001
ALT (U/L)	22.3 ± 13.0	19.1 ± 9.1	16.0 ± 8.3	<0.001
AST (U/L)	25.8 ± 13.8	24.3 ± 8.3	23.7 ± 7.2	0.083
BUN (mg/dL)	16.0 ± 4.5	16.5 ± 5.6	18.1 ± 6.2	<0.001
Creatinine (mg/dL)	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.4	<0.001
GFR (ml/min/1.73 m^2)	75.6 ± 14.8	73.3 ± 17.0	64.3 ± 18.2	<0.001
hsCRP (mg/dL)	0.18 ± 0.57	0.23 ± 0.56	0.37 ± 0.87	0.007

BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, ADL; activity of daily living, IADL; instrumental activity of daily living, WBC; white blood cell, RDW; red cell distribution width, TIBC; total iron-binding capacity, ESR; erythrocyte sedimentation rate, ALT; alanine transaminase, AST; aspartate transaminase, BUN; blood urea nitrogen, GFR; glomerular filtration rate, hsCRP; high-sensitivity C-reactive protein