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Anemia and incidence of dementia in patients with new-onset type 2 diabetes: a nationwide population-based cohort study

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ABSTRACT

Introduction This study aimed to examine the association between anemia and the incidence of dementia in patients with new-onset type 2 diabetes.

Research design and methods This study used the Korean National Health Insurance Service-Health Screening Cohort and included 32 590 participants aged ≥40 years who were diagnosed with new-onset type 2 diabetes between 2004 and 2007 and followed up until 2013. Anemia was defined according to the criteria provided by the WHO, hemoglobin <120 g/L for women and <130 g/L for men, and was measured from after diagnosis date of type 2 diabetes to 2007. Dementia was defined by the Classification of Diseases 10th revision code as primary diagnosis and was measured from after hemoglobin measurement to 2013. We calculated the adjusted HR (AHR) and 95% CI to assess the risk of dementia using multivariable Cox proportional hazards regression models.

Results We identified 1682 patients who developed dementia within a 7.5-year follow-up. Among patients with type 2 diabetes, patients with anemia were associated with an increased risk of dementia than those without anemia (AHR, 1.21; 95% CI 1.06 to 1.39). Patients with mild (AHR, 1.18; 95% CI 1.03 to 1.38) and moderate (AHR, 1.39; 95% CI 1.06 to 1.83) anemia were associated with an increased risk of dementia than those without anemia among patients with type 2 diabetes. Men (AHR, 1.47; 95% CI 1.16 to 1.83) and middle-aged adults (AHR, 1.31; 95% CI 1.03 to 1.75) with anemia were associated with an increased risk of dementia than their counterparts without anemia among patients with type 2 diabetes.

Conclusions Our findings suggest that anemia is significantly associated with an increased risk of dementia among patients with newly diagnosed type 2 diabetes.

Significance of this study

What is already known about this subject?

- Type 2 diabetes is associated with an increased incidence of dementia.
- Anemia frequently occurs in patients with type 2 diabetes and is associated with a decline in cognitive function and increased risk of developing dementia.

What are the new findings?

- Among patients with newly diagnosed type 2 diabetes, patients with anemia were associated with an increased risk of dementia than those without anemia.
- Among patients with type 2 diabetes, patients with mild or moderate anemia were independently associated with a higher incidence of dementia than those without anemia.
- Among patients with type 2 diabetes, men and middle-aged adults with anemia were associated with an increased risk of developing dementia than their counterparts without anemia.

How might these results change the focus of research or clinical practice?

- Anemia is a modifiable factor, and careful survey and optimal management of this disease in patients with type 2 diabetes may be a helpful and applicable way to prevent dementia partially.

INTRODUCTION

Type 2 diabetes and dementia are main chronic conditions with increasing prevalence in Korea and worldwide and are anticipated to have considerable effects on the aging population.[1–4] Previous evidence suggests that type 2 diabetes is related to a decline in cognitive function and the incidence of dementia.[5–11] It has been hypothesized that insulin resistance and hyperglycemia affect cerebrovascular pathologies; however, the underlying mechanisms remain unclear.[12 13] Furthermore, the number of people with dementia is increasing rapidly and is estimated to reach 82 million in 2030 and 152 million in 2050.[14] Although dementia has important economic and social implications and the total global social cost for managing dementia was estimated to be US$818 billion in 2015,[15] there is no specific treatment for dementia in patients with type 2 diabetes. It is, therefore, significant to explore the risk factors for incident dementia among patients with type 2 diabetes.

Anemia has been defined as having hemoglobin concentration lower than 130 g/L and 120 g/L in men and women, respectively.[16]

There is an increasing interest regarding the role of anemia in the development of dementia in the general population.[16–25] A chronic brain hypo-oxygenation due to anemia could be the biological mechanism underlying this association.[17] A significant reduction in brain oxygenation results in reversible cognitive impairment[26]; conversely, an increase in the circulating blood oxygen levels improves cognitive performance. A double-blind, placebo-controlled study implied improvement in cognitive performance following oxygen administration.[27]

Previous studies evaluating the association between anemia and dementia have been performed in general[16 21 22 25] or specific population, such as patients with chronic kidney disease (CKD)[23] or in older adults,[17–20 24] but data on the relationship between anemia and the risk of incident dementia in patients with type 2 diabetes are limited. Anemia frequently occurs in patients with type 2 diabetes,[28] and previous study reported that the risk of anemia in patients with diabetes is approximately two to three times higher than that of a general population.[29] The underlying mechanisms may be due to features of the diabetic milieu (systemic inflammation, functional hematinic deficiencies, resistance of bone marrow to erythropoietin, and red cell abnormalities) that cause hemoglobin levels to drop.[30] Considering that patients with diabetes may be more vulnerable to anemia and that anemia was a major risk factor for dementia, the evidence for association between anemia and dementia among patients with type 2 diabetes needed to be investigated.

This study, therefore, aimed to examine the association between anemia and the incidence of dementia in patients with newly diagnosed type 2 diabetes using nationwide population-based cohort data. We also aimed to identify the risk of dementia development according to the severity of anemia and explore the relationship between anemia and incidence of dementia stratified by sex and age groups.

MATERIALS AND METHODS

Data and study sample

We used data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) database.[31] The NHIS is the sole insurance provider in Korea and covers almost all citizens. All enrollees of the insurance system aged ≥40 years are entitled to standard medical examinations biennially that include a questionnaire survey on lifestyle and medical history, height, weight, and blood pressure (BP) measurements, and laboratory tests. The NHIS-HEALS data were obtained from the 2002–2003 health screening participants who were aged between 40 and 79 years in 2002 and were followed up until 2013. The NHIS-HEALS consisted of 514 866 health screening participants, who accounted for approximately 10% of all health screening participants in 2002 and 2003 by simple random sampling. This database includes patients' demographic characteristics and clinical information concerning treatments, diagnoses, and prescribed drugs of all visits (outpatient, inpatients, and pharmacy visits) provided by healthcare facilities. Moreover, it is connected to the Korean death registration database, which includes dates and causes of deaths.

Of the 513 268 patients who were included in the 2004–2007 NHIS-HEALS database, we excluded those with type 1 diabetes from 2002 to 2007 (n=6629). Moreover, we excluded patients without type 2 diabetes to enroll those who were diagnosed with type 2 diabetes from 2004 to 2007 as study participants (n=425 161). Type 2 diabetes (n=81 478) was defined as the existence of at least one of the following criteria: (1) fasting blood glucose level of ≥126 mg/dL (7 mmol/L), (2) at least one additional diagnosis of type 2 diabetes within 6 months from the initial date of diagnosis under the ICD-10 codes E11–E14, and (3) use of oral hypoglycemic agents or insulin. In subjects who were diagnosed with type 2 diabetes between 2004 and 2007 (baseline period), we excluded those who were diagnosed with type 2 diabetes before the baseline period to recruit only those with newly diagnosed type 2 diabetes (n=40 914). Additionally, we excluded study patients who had a history of dementia before hemoglobin measurement to minimize reverse causality (n=176) and individuals who had no health screening data after diabetes diagnosis (n=7792) or missing data regarding hemoglobin (n=6). The final study sample included 32 590 patients with new-onset type 2 diabetes (online supplementary figure 1).

Measurement

The outcome variable in this study is dementia. Dementia was measured by ICD-10 codes (F00, F01, F02, F03, G30, or G31) as primary diagnosis[32] and was measured from after hemoglobin measurement between 2004 and 2007 until December 31, 2013. This definition of dementia incidence was applied to outpatients and inpatients.

We used anemia as the independent variable, which was defined according to the WHO criteria, hemoglobin <120 g/L for women and <130 g/L for men,[33] and anemia was measured from after diagnosis date of type 2 diabetes to 2007. The severity of anemia was categorized as mild (hemoglobin ≥110 g/L), moderate (hemoglobin 80–109 g/L), or severe (hemoglobin <80 g/L) according to the WHO criteria. Serum hemoglobin concentration was estimated using the cyanmethemoglobin method.

Potential confounding factors were age, sex, body mass index (BMI), systolic and diastolic BP, fasting glucose, total cholesterol, smoking, heavy drinking, exercise, household income, residential area, and comorbidities. The potential confounding factors except for comorbidities were measured on the date of hemoglobin measurement, while comorbidities were measured by screening information for all medical records from January 1, 2002 to the date of hemoglobin measurement. Age was measured as time scale in the Cox proportional hazards models. BP was estimated with the individuals seated following at least 5 min of rest. Total cholesterol and fasting glucose were estimated by blood samples following

overnight fasting. The participants were divided into the following age groups: middle-aged (40–64 years) and older adults (≥65 years). The WHO recommendations for Asian populations were used to categorize individuals into five BMI groups: <18.5 kg/m^2 (underweight), 18.5–22.9 kg/m^2 (normal), 23.0–24.9 kg/m^2 (overweight), 25.0–29.9 kg/m^2 (class I obese), or ≥30 kg/m^2 (class II obese).[34] Regarding smoking status, participants were classified as current smokers, ex-smokers, or non-smokers. Individuals who consumed ≥30 g/day of alcohol were classified as heavy drinkers.[35] Exercise was defined as performing exercise at least once a week. Household income was classified as follows: (1) low income (<40th percentile), (2) middle income (41st–80th percentile),

Table 1 General characteristics of the study participants according to incidence of anemia

		Anemia				
		Yes		No		
Variables	Total	n	%	n	%	P value
Total	32590	3104	9.5	29486	90.5	
Women	12040	1731	55.8	10309	35.0	<0.001
Age (years)						<0.001
40–64	24635	1771	57.1	22864	77.5	
≥65	7955	1333	42.9	6622	22.5	
BMI (kg/m^2)						<0.001
≤18.5	609	177	5.7	432	1.5	
18.5–23	8985	1278	41.2	7707	26.1	
23–25	8645	719	23.2	7926	26.9	
25–30	12769	840	27.1	11929	40.5	
≥30	1582	90	2.9	1492	5.1	
BP (mm Hg)						
Systolic	130.8±17.1	127.7	17.8	131.1	17.0	<0.001
Diastolic	81.0±11.0	77.6	11.1	81.4	10.9	<0.001
Fasting glucose (mg/dL)	132.6±46.3	129.4	49.2	132.9	46.0	<0.001
Total cholesterol (mg/dL)	202.5±40.7	190.2	41.5	203.8	40.4	<0.001
Current smokers	7297	469	15.1	6828	23.2	<0.001
Heavy drinkers	2007	128	4.1	1879	6.4	<0.001
Exercisers	15177	1208	38.9	13969	47.4	<0.001
Household income						<0.001
Low	10155	1184	38.1	8971	30.4	
Middle	12461	1070	34.5	11391	38.6	
High	9974	850	27.4	9124	30.9	
Residential area						<0.001
Metropolitan	4825	383	12.3	4442	15.1	
Urban	8962	843	27.2	8119	27.5	
Rural	18803	1878	60.5	16925	57.4	
Comorbidities						
Hypertension	15048	1527	49.2	13521	45.9	<0.001
Dyslipidemia	11666	1141	36.8	10525	35.7	0.240
CKD	245	56	1.8	189	0.6	<0.001
Ischemic heart disease	5339	625	20.1	4714	16.0	<0.001
Stroke	1725	240	7.7	1485	5.0	<0.001
Depressive disorders	2990	395	12.7	2595	8.8	<0.001
Cancer	2522	397	12.8	2125	7.2	<0.001

Values are presented as mean±SD or n (%).
BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease.

or (3) high income (81st–100th percentile). Residential area was classified as metropolitan (capital), urban (local government with >1 million residents), or rural (otherwise). Comorbidities included hypertension (ICD-10: I10–I15), dyslipidemia (ICD-10: E78), CKD (ICD-10: N18), stroke (ICD-10: I60–I63), ischemic heart disease (ICD-10: I20–I25), depressive disorders (ICD-10: F32–F33), and cancer (ICD-10: C00–C99).

Statistical analysis

Patients' demographic and clinical characteristics were compared according to the presence of anemia using an independent t-test for continuous variables and Pearson's χ^2 test for categorical variables, respectively. Data are expressed as mean±SD for continuous variables or as numbers with percentages for categorical variables. We measured age-standardized incidence rates (95% CI) of dementia per 1000 person-years according to presence or severity of anemia. For each study participant, risk of dementia was estimated from the date of hemoglobin measurement after diabetes diagnosis between 2004 and 2007 until December 31, 2013. The length of follow-up was measured in days, and all study participants were followed up until the onset of dementia, withdrawal from the insurance system, death from any causes, or the end of 2013, whichever occurred first.

We calculated the adjusted HR (AHR) and 95% CI to determine the association between anemia and the incidence of dementia using Cox proportional hazards regression models. First, we analyzed the effect of anemia on the incidence of dementia in patients with new-onset type 2 diabetes. Second, we also identified the risk of dementia according to the severity of anemia. Finally, we explored the relationship between anemia and the incidence of dementia stratified by sex and age groups.

All data extraction and statistical analyses were performed using SAS V.9.4 software. Proportional hazards assumptions were evaluated statistically and satisfied for all models.

RESULTS

Our study enrolled 32 590 patients with new-onset type 2 diabetes aged ≥40 years and observed 1682 events of dementia during an average of 7.5±1.7 years of follow-up. Table 1 shows the general characteristics of the study participants according to the severity of anemia. The proportions of women (55.8% vs 35.0%), older adults (42.9% vs 22.5%), underweight participants (5.7% vs 1.5%), participants with low household income (38.1% vs 30.4%), participants living in rural areas (60.5% vs 57.4%), and participants with comorbidities (hypertension (49.2% vs 45.9%), CKD (1.8% vs 0.6%), ischemic heart disease (20.1% vs 16.0%), stroke (7.7% vs 5.0%), depressive disorders (12.7% vs 8.8%), and cancer (12.8% vs 7.2%)) with anemia were significantly higher than those without anemia among patients with type 2 diabetes. The average systolic (127.7 mm Hg vs 131.1 mm Hg) and diastolic (77.6 mm Hg vs 81.4 mm Hg) BP, fasting glucose (129.4 mg/dL vs 132.9 mg/dL), and total cholesterol (190.2 mg/dL vs 203.8 mg/dL) and the proportions of current smokers (15.1% vs 23.2%), heavy drinkers (4.1% vs 6.4%), and exercisers (38.9% vs 47.4%) with anemia were significantly lower than those without anemia among patients with type 2 diabetes.

Table 2 presents the AHR and 95% CI for the incidence of dementia according to the presence and severity of anemia among patients with newly diagnosed type 2 diabetes. After adjusting for sex and age, model 1 showed that patients with anemia were at a higher risk of dementia (AHR, 1.35; 95% CI 1.18 to 1.53) than those without anemia among patients with type 2

Table 2 Association between anemia and incidence of dementia in patients with new-onset type 2 diabetes

Model	Variables	n	Events	Person-years	Age-standardized incidence rates (95% CI) of dementia per 1000 person-years	HR (95% CI)		
						Model 1†	Model 2‡	Model 3§
Model 1	Anemia							
	No	29 486	1396	221 429	43 (41 to 45)	1.00		
	Yes	3104	286	21 828	73 (66 to 79)	1.35 (1.18 to 1.53)***	1.33 (1.12 to 1.51)***	1.21 (1.06 to 1.39)*
Model 2	Severity of anemia							
	None	29 486	1396	221 429	43 (41 to 45)	1.00		
	Mild	2484	224	17 618	71 (64 to 78)	1.32 (1.13 to 1.51)***	1.30 (1.11 to 1.49)**	1.18 (1.03 to 1.38)*
	Moderate	584	61	3972	81 (65 to 98)	1.58 (1.21 to 2.05)***	1.55 (1.24 to 2.01)***	1.39 (1.06 to 1.83)*
	Severe	36	1	238	43 (1 to 87)	0.69 (0.11 to 5.07)	0.63 (0.11 to 4.74)	0.68 (0.10 to 4.87)

*P<0.05, **P<0.01, ***P<0.001.
†HRs were estimated after adjusting for sex and age.
‡HRs were estimated after adjusting for sex, age, household income, and residential area.
§HRs were estimated after adjusting for sex, age, body mass index, blood pressure, fasting glucose, total cholesterol, smoking, heavy alcohol drinking, exercise, household income, residential area, and comorbidities.

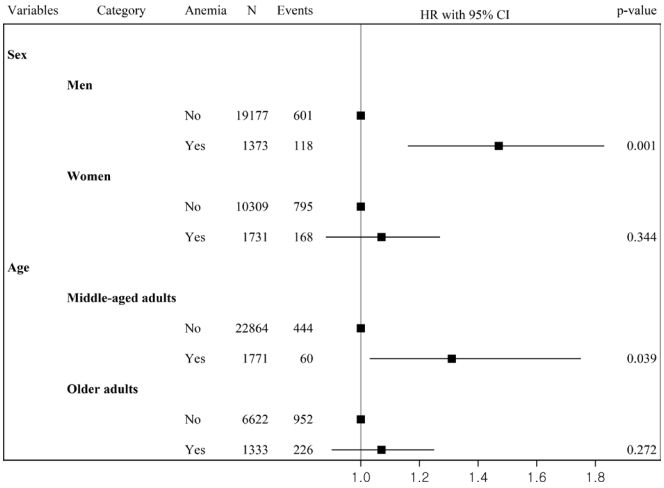

Figure 1 Association between anemia and incidence of dementia according to sex and age.

diabetes. Among patients with type 2 diabetes, the risk of dementia was significantly higher in patients with mild (AHR, 1.32; 95% CI 1.13 to 1.51) and moderate (AHR, 1.58; 95% CI 1.21 to 2.05) anemia than those without anemia. After adjusting for sex, age, residential area, and household income, model 2 revealed that patients with anemia were at a higher risk of dementia (AHR, 1.33; 95% CI 1.12 to 1.51) than those without anemia among patients with type 2 diabetes. Among patients with type 2 diabetes, the risk of dementia was significantly higher in patients with mild (AHR, 1.30; 95% CI 1.11 to 1.49) and moderate (AHR, 1.55; 95% CI 1.24 to 2.01) anemia than those without anemia. After adjusting for all potential confounding factors, model 3 indicated that patients with anemia were at a higher risk of dementia (AHR, 1.21; 95% CI 1.06 to 1.39) than those without anemia among patients with type 2 diabetes. Among patients with type 2 diabetes, the risk of dementia was significantly higher in patients with mild (AHR, 1.18; 95% CI 1.03 to 1.38) and moderate (AHR, 1.39; 95% CI 1.06 to 1.83) anemia than those without anemia. However, there was no significant association between severe anemia and risk of developing dementia in all models.

Figure 1 shows the results of the analysis of the association between anemia and the incidence of dementia according to sex and age. Among men with type 2 diabetes, patients with anemia were at a higher risk of dementia (AHR, 1.47; 95% CI 1.16 to 1.83) than those without anemia. In middle-aged adults with type 2 diabetes, the risk of dementia increased significantly in patients with anemia than those without (AHR, 1.31; 95% CI 1.03 to 1.75). In women and older adults, there was no statistically significant association between anemia and the incidence of dementia.

DISCUSSION

This study had three main findings. First, among patients with newly diagnosed type 2 diabetes, patients with anemia were associated with an increased risk of dementia than those without anemia. Second, among patients with type 2 diabetes, patients with mild or moderate anemia were associated with an increased risk of dementia development than those without anemia. Third, among patients with type 2 diabetes, men and middle-aged adults with anemia were associated with an increased risk of dementia than their counterparts without anemia.

Our findings were in line with previous studies which had investigated the association between anemia and dementia,[16–22 24 25] except for a research on patients with CKD.[23] Although the mechanisms linking anemia to the incidence of dementia have not been fully established, a few hypotheses have been suggested. First, chronic brain hypoxia associated with anemia may affect patients' cognitive function by expediting the accumulation of amyloid-β.[36] Second, anemia has been related to the progression of white matter disease.[37] A meta-analysis study showed a significant relationship between white matter hyperintensities and the incidence of dementia. Finally, anemia associated with deficiency in micronutrients such as vitamin B_{12} and iron may be related to dementia.[20] Iron deficiency (a mineral that plays a critical role in storage and transport of oxygen in the brain) may cause cognitive decline or cerebral hypoxia.[38] Deficiency in vitamin B_{12} has also been associated with dementia.[39]

Our findings showed that patients with mild or moderate anemia had higher incidence of dementia than those without anemia. Furthermore, the age-standardized incidence rate of dementia of moderate anemia (0.081) was higher than that of mild anemia (0.071). Previous research verified that patients with lower hemoglobin concentration had a higher AHR value of incident dementia.[17] Another study showed that severe anemia was independently related to the incidence of dementia.[24] These findings support the notion that the risk of developing dementia increases when the hemoglobin concentration decreases. One potential mechanism that can possibly explain the dose–response association is that mild anemia may have lesser effect on oxygen delivery to the brain through a compensatory reaction, such as vascular dilation, to maintain the cerebral blood flow than moderate or severe anemia.[40]

Although the prevalence of anemia and dementia is more frequent in women than in men,[24] our findings showed that anemia was independently associated with the incidence of dementia in men with type 2 diabetes, which is different from results in previous studies conducted in the general population. Denny *et al*[18] suggested that the effect of anemia on dementia is greater in women than in men. Chung *et al*[21] found that female, and not male, patients with dementia had higher prevalence of iron deficiency anemia. Our results also showed a significant association between anemia and the incidence of dementia in middle-aged adults with type 2 diabetes. Anemia and dementia commonly occur in older adults,[41 42] and previous studies showed significant relationship between anemia and dementia among older adults.[17–20 24] In patients with type 2 diabetes, our

findings suggest that men and middle-aged adults with anemia were significantly associated with risk of dementia compared with their counterparts without anemia, respectively.

Our study had several limitations that need to be considered. First, we could not determine the severity of dementia from the medical records. Second, although we examined the incidence of dementia according to the severity of anemia, only one case of severe anemia was associated with incidence of dementia. Future research is warranted to explore the association between severe anemia and dementia using larger data. Third, although we excluded patients with a dementia diagnosis made before the date of anemia measurement, there may have been reverse causality. Fourth, we were not able to obtain patients' genetic information, such as *APOE4* carrier status, and we were not able to assess their education and literacy levels, which might have an effect on cognitive function.[43] Finally, as the Korean population is predominantly of Asian descent, further studies are needed to confirm that these findings are consistent with other ethnicities and geographical regions.

Despite these limitations, the strengths of our study included its longitudinal design and the abundant available data regarding demographics, lifestyle variables, comorbidities, and biomedical information. To the best of our knowledge, this is the first study to examine the association between anemia and the incidence of dementia among patients with new-onset type 2 diabetes.

In conclusion, this cohort study of the Korean population demonstrated that anemia is significantly associated with an increased risk of dementia among patients with newly diagnosed type 2 diabetes. Anemia is a modifiable factor, and most of its types occur due to insufficient nutrition (vitamins or iron).[44] Moreover, anemia of chronic disease may be modified through treatment (eg, erythropoietin therapy in diabetes).[45] Therefore, we suggest that careful examination and optimal management of anemia in patients with type 2 diabetes may be helpful and applicable methods to partially prevent the development of dementia.

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Contributors JWC and EH designed the study. JWC and THK performed the literature review and interpretation of data analysis. JWC analyzed the data. JWC, THK, and EH wrote the draft. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Yonsei University Institutional Review Board approved this study (approval number: 7001988-202002-HR-792-01E) and the requirement for informed consent was waived as the NHIS-HEALS database was constructed after anonymization according to strict confidentiality guidelines.

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