Psychiatric disorders risk in patients with iron deficiency anemia and association with iron supplementation medications: a nationwide database analysis

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Abstract

Background It has been shown that iron deficiency anemia (IDA) is associated with psychosocial consequences and psychiatric morbidity. However, the association between adults with IDA and psychiatric disorders has not been clarified. The purpose of this study is to investigate the psychiatric disorders morbidity of IDA in comparison with non-IDA group and to examine the risk of psychiatric disorders in IDA patients treated with iron supplementary.Methods All study subjects aged ≥ 20 years with newly diagnosed IDA in the Taiwan National Health Insurance Database during 2000-2012 were enrolled. We matched IDA and non-IDA subjects according to age and gender in a 1:2 ratio. Our primary outcome was diagnosis of psychiatric disorders and the patients were monitored until the end of 2013. The Cox proportional hazards regression model was used to evaluate the risk of psychiatric disorders events to occur in IDA.Results The adjusted hazard ratios (aHR) of psychiatric disorders was 1.49 (95% CI = 1.43 – 1.56) in the IDA group compared with the non-IDA group. Among the different type of psychiatric disorders occurrence, the IDA group was associated with significantly higher incidence and risks of dementia, anxiety disorders, depression, sleep disorders and psychotic disorders ($p < 0.05$). Furthermore, iron supplementation use to IDA subjects was associated with significantly lower risk of psychiatric disorders compared with IDA patients without iron supplementation.Conclusions Our study indicates that IDA had an increased risk of psychiatric disorders, regardless of other confounders. Moreover, in IDA patients, iron supplementation use could reduce the risk of psychiatric disorders, especially sleep disorders.

Background

Iron deficiency is the commonest nutrient deficiencies worldwide, affecting more than two billion people [1]. Iron is an indispensable nutritional element for every living organism. It is essential for numerous important functions, such as transport of oxygen, cellular respiration, immune function, neurotransmitter metabolism and DNA synthesis [2, 3]. The definition of iron deficiency is the decrease of the total content of iron in the body. Iron deficiency anemia (IDA) occurs when iron deficiency is sufficiently severe to subtract erythropoiesis and gives rise to the development of anemia.

An accumulating body of evidence currently indicates that iron has an important role in neurologic functions and developments. IDA give rise to poor myelination in the brain and impairment of the monoamine metabolism [4]. Current literature was indicated that the brain iron deficiency influences neurotransmitter [glutamate and γ-aminobutyric acid (GABA)] homeostasis and then causes deficits in memory, learning, behavior, as well as emotional and psychological problems [5]. In addition, previously research found that anemia patients were more prevalent cognitive derangement and neurological symptoms [6].

There is growing evidence that has been shown that IDA are associated with psychosocial consequences and psychiatric morbidity, including anxiety disorders [7], depression [8], bipolar disorders [7], sleep disorders [9], restless legs syndrome (RLS) [10] and dementia [11]. However, the relationship between IDA

and psychiatric disorders morbidity in adults has not been clarified yet. Therefore, we used a population-based cohort analysis to investigate the psychiatric disorders morbidity of IDA in comparison with non-IDA group and to examine the risk of psychiatric disorders in IDA patients treated with iron supplementary.

Methods

Data sources

This retrospective population-based cohort study used the Longitudinal Health Insurance Database 2005 (LHID 2005) released by the Taiwan National Health Research Institutes (NHRI) for research purposes. The National Health Insurance (NHI) Program implemented on March 1, 1995 covers more than 99% of the 23.74 million population of Taiwan. The LHID2005 comprises a random sample of 1 million of those, and includes the demographic data of enrollees. The LHID 2005 contains the demographic data of enrollees; service records and expenditure claims from outpatient, inpatient, and ambulatory care; and data associated with contracted pharmacies for reimbursement purposes. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes was used to identify diseases in this study. The accuracy of diagnoses in the NHIRD has been verified in previous articles. The study was approved by the Institutional Review Board of the Ditmanson Medical Foundation Chia-Yi Christian Hospital, Taiwan (CYCH-IRB No: 2018078).

Study population

We conducted a retrospective cohort study on the period from January 1, 1996 to December 31, 2013. Patients newly diagnosed with IDA (ICD-9-CM: 280) were selected from the period between January 1, 2000 and December 31, 2012. We selected cases 20 or more years of age with a first diagnosis of IDA from the LHID 2005 between 2000 and 2012. The patients diagnosed with anxiety disorders, depression, psychotic disorders, bipolar disorders, sleep disorders, RLS, dementia before 2000, or before the first visit for IDA, were excluded. In order to increase the validity of IDA diagnoses, this study only included cases that have had at least two diagnoses of IDA in their medical claims prior to their index date as IDA cases. The iron supplementary medication were also collected. Individuals who had missing data, and those who were diagnosed without blood tests were excluded. Moreover, on the basis of the clinical guidelines and health insurance regulations under the NHI, patients suspected of having IDA might receive a diagnosis of unspecified anemia (ICD-9-CM: 285) on the first visit. However in order to a definite diagnosis of IDA the patient must be confirmed by receiving the laboratory test (decreased serum iron and ferritin, increased total iron binding capacity [TIBC]). We matched IDA and non-IDA subjects according to age and gender in a 1:2 ratio.

Main Outcome

Patients in both the IDA and non-IDA groups were followed up from the index date until the end of December 31, 2013 or until one of the following events occurred: diagnosis with psychiatric disorders,

including anxiety disorders ICD-9-CM: 300), depression (ICD-9-CM: 296.2-296.3, 300.4 and 311), psychotic disorders (ICD-9-CM: 295 and 297-298), bipolar disorders (ICD-9-CM: 296.0, 296.4-296.8), sleep disorders (ICD-9-CM: 307.4 and 780.5), RLS (ICD-9-CM: 333.90 and 333.99), and dementia (ICD-9-CM: 290, 294.1, and 331.0) withdrawal from the NHI program, or death, whichever came first.

Baseline characteristics and comorbidities

The general characteristics of individuals were comprised age, gender, insurable salary (in New Taiwan Dollars [NT$]; <19,100, 19,100 – 41,999, ≥ 42,000) and urbanization level of residence (levels 1 – 4). The covariates of comorbidities that were selected in this study included hypertension (ICD-9-CM: 401 – 405), diabetes mellitus (DM, ICD-9-CM: 250), dyslipidemia (ICD-9-CM: 272), hyperthyroidism (ICD-9-CM: 242), hypothyroidism (ICD-9-CM: 244), chronic pulmonary disease (COPD, ICD-9-CM: 490 – 496) , stroke (ICD-9-CM: 430 – 438), coronary artery disease (CAD, ICD-9-CM: 410 – 414), chronic kidney disease (CKD, ICD-9-CM: 585) and liver cirrhosis (ICD-9-CM: 571.2, 571.5, and 571.6).

Statistical analysis

Demographic characteristics was expressed using means and standard deviations (SD) for continuous variables, presented as number and percentage for categorical variables. The differences in continuous variables were estimated using t-tests, and differences between categorical variables were analyzed using the chi-square test or Fisher exact test, as appropriate. The incidence rate was calculated as the number of first diagnoses of psychiatric disorders per 1,000 person-years. Hazard ratios (HRs) and 95% confidence interval (CI) for developing outcomes (including overall events and dementia, anxiety disorders, depression, bipolar disorders, sleep disorders, RLS, and psychotic disorders, respectively) were calculated using univariate and multivariate Cox proportional hazards models. Multivariable Cox proportional hazards models were used to explore the associations between IDA and risk of psychiatric disorders, controlling for age, gender, and medical comorbidities. We used the Kaplan-Meier method and log-rank test to estimate the cumulative risks of psychiatric disorders between the IDA and non-IDA groups. A 2-tailed *p*-value of < 0.05 was considered significant. The SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis of the results. Statistical graphs were plotted with R version 3.5.1, with the KMsurv, survfit and survival packages.

Results

Baseline characteristics of the IDA and non-IDA groups

In total, we enrolled 19,397 IDA patients and 38,794 controls. The demographic characteristics and comorbidities of the study population are presented in Table 1. Of the IDA and non-IDA groups, the mean age were 49.08 ± 17.54 and 76.77% were women. The IDA patients had a higher prevalence of listed comorbidities and iron supplementation rate than non-IDA group ($p < 0.05$). In addition, there was a significant difference in the income level and living area ($p < 0.05$) between these two groups.

The risk factors of psychiatric disorders in IDA group

After adjustment for age, gender, level income, comorbidities, iron supplementation and area, the adjusted HR (aHR) of psychiatric disorders was 1.49 (95% CI = 1.43 – 1.56) in the IDA group compared with the non-IDA group (Table 2). Additionally, figure 1 reveals that the incidence of psychiatric disorders was higher in IDA group compared with the non-IDA group (log-rank test $p < 0.001$). A multivariate Cox proportional hazards analysis identified older age, female, low income, hypertension, DM, dyslipidemia, hyperthyroidism, COPD, stroke, CAD, CKD, cirrhosis and non-iron supplementation as independent risk factors of psychiatric disorders.

Type of psychiatric disorders after IDA

Among the different type of psychiatric disorders occurrence, the IDA group was associated with significantly higher incidence and risks of anxiety disorders (aHR = 1.47, 95 % CI = 1.33 – 1.63, $p < 0.001$), depression (aHR = 1.49, 95 % CI = 1.33 – 1.66, $p < 0.001$), psychotic disorders (aHR = 1.41, 95 % CI = 1.07 – 1.86, $p < 0.050$), sleep disorders (aHR = 1.53, 95 % CI = 1.46 – 1.61, $p < 0.001$) and dementia (aHR = 1.29, 95 % CI = 1.15 – 1.44, $p < 0.001$) (Table 3).

The risk of psychiatric disorders in the IDA group with or without iron supplementation

After adjusted the confounding factors, iron supplementation use to IDA subjects was associated with significantly lower risk of psychiatric disorders compared with IDA patients without iron supplementation (aHR = 0.86, 95% CI = 0.81 – 0.91). In addition, IDA patients with iron supplementation group had a significantly lower risk of sleep disorders than IDA patients without iron supplementation use group (aHR = 0.84, 95 % CI = 0.79 – 0.89, $p < 0.001$, Table 4).

Stratification by gender for the risk of psychiatric disorders

Table 5 displays the gender stratification analysis of the risk of IDA-association psychiatric disorders. We demonstrated that IDA patients with or without iron supplementation had a higher risk of psychiatric disorders compared with non-IDA group (irrespective of sex, $p < 0.05$).

Discussion

This nationwide population-based cohort study indicated IDA is a potential risk factor for developing psychiatric disorders, even after adjusting for age, gender, income, urbanization and comorbidities. Among the different psychiatric disorders, our results also revealed that the IDA subjects were associated with an increased risks of dementia, anxiety disorders, depression, sleep disorders and psychotic disorders. Furthermore, the IDA patients with iron supplementation were associated with significantly lower risks of psychiatric disorders, especially sleep disorders.

The current study demonstrated that IDA was associated with a significantly increased risk of dementia, anxiety disorders, depression, sleep disorders and psychotic disorders. Our results are generally

consistent with the findings of previous studies [7-9, 11, 12]. A case-control study indicated that women with dementia had a higher prevalence of prior IDA, compared to controls [11]. Three studies suggested that patients with IDA have a higher risk of psychiatric disorders [7, 8, 12]. In addition, a cross-sectional study showed that IDA affects sleep quality irrespective of psychological symptoms such as depression and anxiety [9]. However, some studies concluded that there was no association between IDA and psychotic disorders. A cohort study was reported no increased risk of dementia/cognitive decline in anemia patients in the US [13]. Yi et al. and Millingen et al. showed no association between IDA and depression [13, 14]. This inconsistency may be due to the heterogeneous study designs, sample selection criteria, or ethnic differences. Nevertheless, these research tend to small-scale, cross-sectional or case-control design. Our study used a large population-based dataset and longitudinal design. And it can reduce possible surveillance bias and enables the consideration of possible confounders for the development of psychiatric disorders. Such study design can more supports the association between IDA and psychiatric disorders.

Previous studies have been reported to show iron effects on the brain activity and mood presentation [5, 15, 16]. Iron is involved in many neurological activities and deficiency is associated with anxiety and depressive symptoms as well as developmental problems [2, 5]. In the present study, iron supplementation was shown a beneficial effect on the psychiatric disorders. We found that iron supplementation to non-IDA female subjects were associated with significantly lower risks of psychiatric disorders. Our results also found that iron supplementation was benefit for reducing sleep disorders risks in with IDA patients. Similar to our finding, a study in Japan demonstrated that iron intake could reduce the risk of depression [12]. Another research in Korean found depression was negatively associated with intake of iron after adjusting for confounding variables [17]. A meta-analysis also indicated an inverse association between dietary iron intake and risk of depression [18]. Moreover, a couple of studies also indicated that higher iron intake has a beneficial effect on the lower risks of depressive symptoms [17, 19]. Several mechanisms are suggested for the relationship between iron deficiency and psychiatric disorders. Iron deficiency results in an alteration of monoamine neurotransmitters and the abnormal myelination of white matter [20, 21]. Glutamate and GABA homeostasis is modified by fluctuations in brain iron status [22]. Such alterations bring about emotional and psychological problems. Iron is essential for a number of enzymes involved in neurotransmitter synthesis, including serotonin, dopamine and norepinephrine [23]. These neurotransmitters are involved in the regulation of mood, neuronal activity, and anxiety. Iron deficiency is usually associated with low level of serotonin. Previous studies have shown that serotonin deficiency may cause a relapse in patients with depression [24, 25]. In addition, evidence has shown that impaired emotional behaviors are associated with iron deficiency via modified dopamine metabolism [26-28]. Therefore, these possible biological mechanisms may explain why iron intake could reduce the risk of psychiatric disorders.

In present study, the developing psychiatric disorders in IDA patients with or without iron supplementation use is significantly higher than non-IDA group. The results are similar to Hong et al. research. They found IDA patient inclined to display higher risk of Parkinson's disease, which remained unaffected by iron supplementation [29]. The possible reason may be due to non-responsiveness to iron therapy in some

patients with IDA [30]. In addition, patients with IDA, inflammation or other coexisting conditions may block the intestinal iron absorption and inhibit iron release from stores [31]. Therefore, even if IDA patients with iron supplementation use also have higher psychiatric disorders compared non-IDA group.

Strengths And Limitations

The advantages of our study is taken a large sample size. It can provide adequate statistical power to elucidate this important theme and can also avoid selection bias. However, this study had the several insufficiencies that should be addressed. First, some important information on psychological status, nutrition status, sleep quality, lifestyle factors, and individual behavior, is not recorded in the NHIRD. These might be confounding factors in this study. Second, the prevalence of psychiatric disorders was likely to be underestimated because only the subjects who used the medical resource to seek psychiatric help were identified. Finally, it would be difficult to assess the influence of iron deficiency or IDA severity on the psychiatric disorders risk in this study. Consecutive studies would be necessary to explain the possible relationship between psychiatric disorders and iron deficiency or IDA severity.

Conclusions

In conclusion, our study provides epidemiological evidence that IDA may play a role in increasing the risk of psychiatric disorders. Moreover, in IDA patients, iron supplementation use could reduce the risk of psychiatric disorders, especially sleep disorders. Further study is required to clarify the mechanisms in the association between IDA and psychiatric disorder.

Abbreviations

AHR: Adjusted hazard ratios; CAD: Coronary artery disease; CI: confidence interval; CKD: Chronic kidney disease; COPD: Cchronic pulmonary disease; DM: Diabetes mellitus; GABA: glutamate and γ-aminobutyric acid; HRs: Hazard ratios; ICD-9-CM: International Classification of Disease, 9th Revision, Clinical Modification; IDA: Iron deficiency anemia; LHID 2005: Longitudinal Health Insurance Database 2005; NHI: National Health Insurance; NHIRD: National Health Research Institutes; NT: New Taiwan Dollars; RLS: restless legs syndrome; SD: Standard deviations; TIBC: total iron binding capacity

Declarations

Ethics approval and consent to participate

This study have been reviewed and approved by the Institutional Review Board of the Ditmanson Medical Foundation Chia-Yi Christian Hospital, Taiwan (CYCH-IRB No: 2018078). Because this was a secondary data analysis, all identifications of patients and institutions in NHIRD have been removed before data release, the informed consent was not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). Any researcher interested in accessing this dataset can submit an application form to the MOWH requesting access. Please contact the staff of MOHW (Email: wt.vog.whom@uwloracts) for further assistance. Taiwan MOHW address: No. 488, Sec. 6, Zhongxiao E. Road, Nangang District, Taipei City 115, Taiwan. Phone: +886 2 8590 6848.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors contributed to the design of the study, interpretation of the results and development of the final manuscript. HSL, HHC, and HYY conceived the study. HYY and WTH collated the data and performed the statistical analyses. HYY, SCCC and HSL criticized and revised manuscript content. HSL, HHC, and HYY wrote the manuscript with contributions from all coauthors.

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Tables

Table 1 Baseline demographic factors and comorbidity of study participants according to IDA

	IDA Group N = 19,397	Non-IDA Group N = 38,794	*p*-value
Age	49.08 (17.54)	49.08 (17.54)	0.999
≦ 50	12024 (61.99)	24069 (62.04)	
> 50	7373 (38.01)	14725 (37.96)	
Gender			1.000
Female	14891 (76.77)	29782 (76.77)	
Male	4506 (23.23)	9012 (23.23)	
Income level			< 0.001
Low	9366 (48.29)	19247 (49.61)	
Intermediate	8604 (44.36)	16523 (42.59)	
High	1427 (7.36)	3024 (7.80)	
Comorbidity			
Hypertension	4991 (25.73)	7874 (20.30)	< 0.001
DM	2719 (14.02)	3529 (9.10)	< 0.001
Dyslipidemia	2822 (14.55)	4435 (11.43)	< 0.001
Hyperthyroidism	551 (2.84)	752 (1.94)	< 0.001
Hypothyroidism	199 (1.03)	257 (0.66)	< 0.001
COPD	3618 (18.65)	5606 (14.45)	< 0.001
Stroke	1642 (8.47)	2235 (5.76)	< 0.001
CAD	2490 (12.84)	3594 (9.26)	< 0.001
CKD	888 (4.58)	412 (1.06)	< 0.001
Cirrhosis	566 (2.92)	216 (0.56)	< 0.001
Iron supplementation	12450 (64.19)	1551 (4.00)	< 0.001
Area			< 0.001
Urban	11393 (58.74)	23754 (61.23)	
Suburban	5974 (30.80)	11479 (29.59)	
Rural	1286 (6.63)	2216 (5.71)	
Remote area	744 (3.84)	1345 (3.47)	

Data are presented as mean ± SD or number (percentage, %). DM, Diabetes mellitus; CAD, Coronary artery disease; CKD, Chronic kidney disease; COPD, Chronic Obstructive Pulmonary Disease.

Table 2 Univariate and multivariate analyses of risk factors for psychiatric disorders

	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
IDA	1.36 (1.31 - 1.40)	< 0.001	1.49 (1.43 - 1.56)	< 0.001
Age				
≦ 50	1.00		1.00	
> 50	1.30 (1.26 - 1.34)	< 0.001	1.21 (1.16 - 1.26)	< 0.001
Gender				
Female	1.00		1.00	
Male	0.82 (0.79 - 0.86)	< 0.001	0.69 (0.66 - 0.72)	< 0.001
Income level				
Low	1.00		1.00	
Intermediate	0.94 (0.91 - 0.98)	0.001	0.98 (0.95 - 1.01)	0.204
High	0.78 (0.73 - 0.83)	< 0.001	0.87 (0.81 - 0.94)	< 0.001
Comorbidity				
Hypertension	1.46 (1.41 - 1.51)	< 0.001	1.19 (1.13 - 1.25)	< 0.001
DM	1.27 (1.20 - 1.33)	< 0.001	0.90 (0.85 - 0.96)	0.001
Dyslipidemia	1.46 (1.39 - 1.53)	< 0.001	1.18 (1.12 - 1.25)	< 0.001
Hyperthyroidism	1.30 (1.17 - 1.44)	< 0.001	1.18 (1.06 - 1.31)	0.002
Hypothyroidism	1.37 (1.15 - 1.63)	< 0.001	1.12 (0.94 - 1.33)	0.211
COPD	1.40 (1.34 - 1.46)	< 0.001	1.21 (1.16 - 1.27)	< 0.001
Stroke	1.53 (1.44 - 1.62)	< 0.001	1.15 (1.07 - 1.23)	< 0.001
CAD	1.55 (1.48 - 1.63)	< 0.001	1.17 (1.11 - 1.24)	< 0.001
CKD	1.24 (1.11 - 1.37)	< 0.001	0.88 (0.79 - 0.98)	0.026
Cirrhosis	0.95 (0.81 - 1.11)	0.498	0.80 (0.68 - 0.93)	0.005
Iron supplementation	1.13 (1.09 - 1.17)	< 0.001	0.83 (0.79 - 0.87)	< 0.001
Area				
Urban	1.00		1.00	
Suburban	1.01 (0.97 - 1.05)	0.67	0.99 (0.95 - 1.02)	0.401
Rural	1.00 (0.93 - 1.07)	0.918	0.92 (0.86 - 0.99)	0.020
Remote area	1.02 (0.94 - 1.12)	0.602	0.96 (0.88 - 1.05)	0.352

DM, Diabetes mellitus; CAD, Coronary artery disease; CKD, Chronic kidney disease; COPD, Chronic Obstructive Pulmonary Disease

Table 3 Incidence, incidence rate ratio and hazard ratio of time until different type of psychiatric disorders between IDA group and non-IDA group

Variables	IDA			Non-IDA				
	Event	PY	Rate†	Event	PY	Rate†	IRR (95% CI)	Adjusted HR‡ (95% CI)
Overall	5800	116292.93	49.87	9190	251123.67	36.60	1.36 (1.33 - 1.40)***	1.50 (1.44 - 1.57)***
Anxiety disorders	1183	143459.13	8.25	1739	291222.14	5.97	1.38 (1.28 - 1.49)***	1.47 (1.33 - 1.63)***
Depression	940	144477.03	6.51	1397	292544.68	4.78	1.36 (1.25 - 1.48)***	1.49 (1.33 - 1.66)***
Psychotic disorders	138	148802.23	0.93	216	298418.90	0.72	1.28 (1.04 - 1.59)*	1.41 (1.07 - 1.86)*
Bipolar disorders	70	149237.96	0.47	130	298949.78	0.43	1.08 (0.81 - 1.44)	1.18 (0.79 - 1.74)
Sleep disorders	4870	121755.17	40.00	7590	259317.13	29.27	1.37 (1.32 - 1.42)***	1.53 (1.46 - 1.61)***
RLS	54	149295.29	0.36	67	299237.33	0.22	1.62 (1.13 - 2.31)**	1.30 (0.80 - 2.12)
Dementia	720	146140.67	4.93	1188	294583.04	4.03	1.22 (1.11 - 1.34)***	1.29 (1.15 - 1.44)***

IRR, incidence rate ratio; PY, person-years; †Rate, incidence rate in per 1,000 person-years; *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$; ‡Adjusted for age, gender, income level, hypertension, DM, dyslipidemia, CAD, stroke, CKD, cirrhosis, hyperthyroidism, hypothyroidism, COPD, iron supplementation and area.

Table 4 The risk of different type of psychiatric disorders in the IDA group with or without iron supplementation

	Crude HR (95% CI)	*p*-value	Adjusted HR‡ (95% CI)	*p*-value
Overall	0.88 (0.83 – 0.92)	< 0.001	0.86 (0.81 – 0.90)	< 0.001
Anxiety disorders	1.00 (0.89 – 1.13)	0.993	0.91 (0.80 – 1.03)	0.129
Depression	0.97 (0.85 – 1.11)	0.967	0.89 (0.77 – 1.02)	0.096
Psychotic disorders	0.88 (0.62 – 1.25)	0.473	0.93 (0.65 – 1.33)	0.686
Bipolar disorders	1.01 (0.74 – 1.39)	0.944	0.96 (0.57 – 1.61)	0.866
Sleep disorders	0.89 (0.84 – 0.95)	< 0.001	0.84 (0.79 – 0.89)	< 0.001
RLS	1.49 (1.02 – 2.17)	0.038	1.45 (0.99 – 2.14)	0.057
Dementia	0.65 (0.56 – 0.76)	< 0.001	0.95 (0.82 – 0.91)	0.499

‡Adjusted for age, income level, hypertension, DM, dyslipidemia, CAD, stroke, CKD, cirrhosis, hyperthyroidism, hypothyroidism, COPD, and area

Table 5 Adjusted HRs measured using multiple Cox proportional model for the patients with psychiatric disorders associated with IDA combines effect of iron supplementation, with stratification by gender

Iron supplementation	IDA	Male		Female	
		Adjusted HR‡ (95% CI)	*p*-value	Adjusted HR‡ (95% CI)	*p*-value
-	-	1.00		1.00	
+	-	0.75 (0.56 – 1.00)	0.053	0.71 (0.63 – 0.79)	< 0.001
-	+	1.39 (1.26 – 1.52)	< 0.001	1.48 (1.40 – 1.57)	< 0.001
+	+	1.12 (1.01 – 1.24)	0.027	1.28 (1.23 – 1.33)	< 0.001

‡Adjusted for age, income level, hypertension, DM, dyslipidemia, CAD, stroke, CKD, cirrhosis, hyperthyroidism, hypothyroidism, COPD, and area

Figures

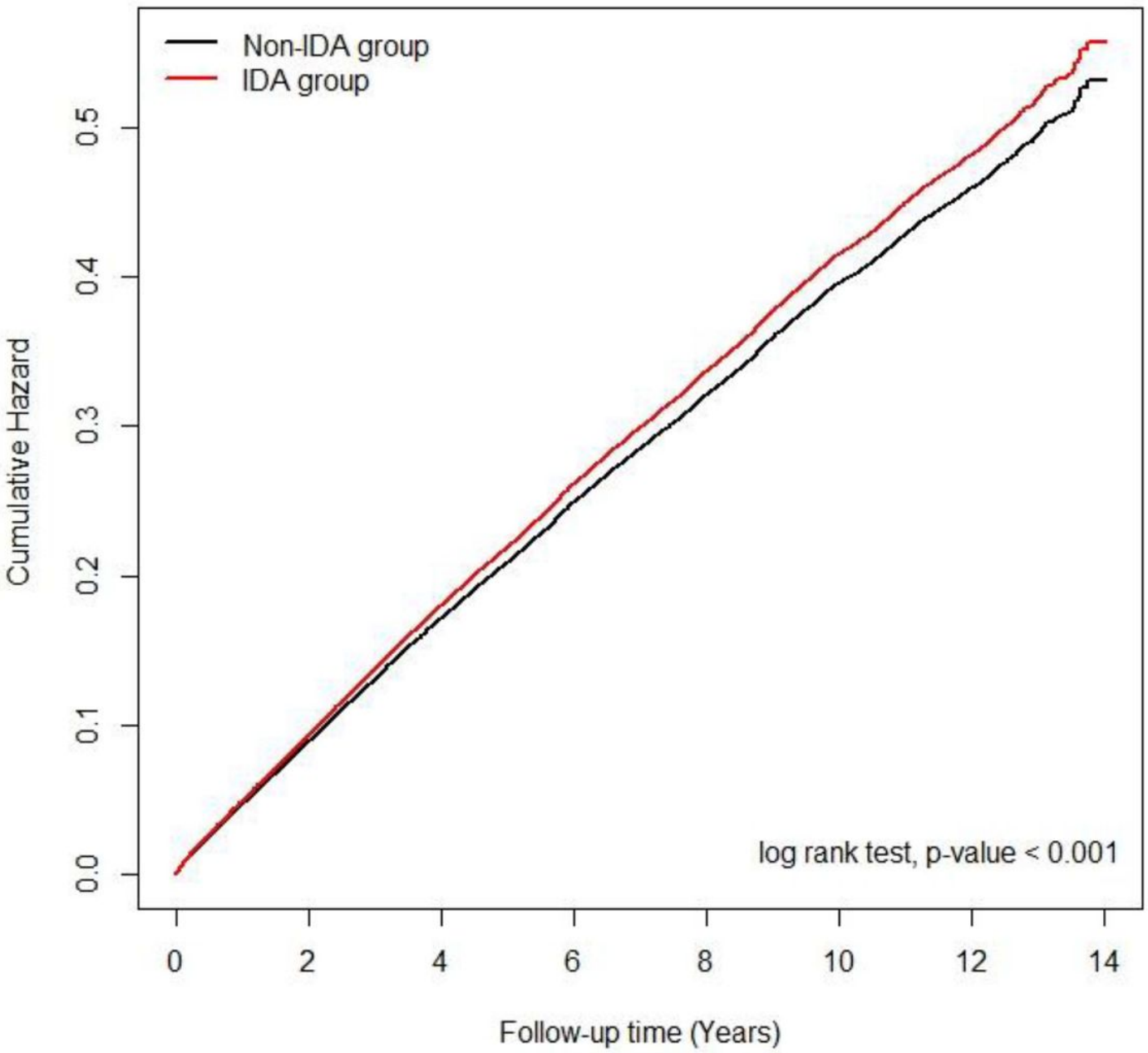

Figure 1

Supplementary Files

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