Association of Anemia with Dementia and Cognitive Decline among Community-Dwelling Elderly

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Abstract

Introduction: The association of anemia with dementia in elders is controversial. We examined the potential association of anemia with dementia in a large population of elders. Methods: Historical-prospective registry-based study. Included 36,951 community-dwelling elders (65–113 years) that were followed during 2002–2012. Anemia of all kinds was defined according to Clalit Health Services (CHS) definitions: hemoglobin (HGB) <14 g/dL men, <12 g/dL women; and World Health Organization (WHO): HGB <13 g/dL men, <12 g/dL women. Anemia was categorized as mild (HGB 11–13 g/dL men, 11–12 g/dL women) or moderate-severe (HGB <8–10.9 g/dL men and women). Background data, laboratory values, and diagnosis of dementia and cognitive decline (DCD) were reviewed. Results: During the 10-year follow-up period, DCD was newly diagnosed in 7,180 subjects (19.4%). Subjects with DCD had a higher rate of anemia than those without DCD. Time to development of DCD was 1.5 years shorter in those with than without anemia. On multivariate Cox regression analysis adjusted for age and sex, the hazard ratio (HR) for DCD was 1.45 (95% CI: 1.37–1.54) by CHS and 1.51 (95% CI: 1.41–1.61) WHO anemia criteria. The more severe the anemia, the greater the risk of DCD development (HGB 13–14 g/dL [men only], HR = 1.20 [95% CI: 1.09–1.32]; mild anemia, HR = 1.38 [95% CI: 1.28–1.49]; moderate-severe anemia, HR = 1.64 [CI: 1.41–1.90]). Every decrease in 1 standard deviation of HGB (1.4 g/dL) increased the DCD risk by 15%. A competing risk model has weakened the association of anemia with DCD risk. Conclusions and implications: Anemia in community-dwelling elders appears to be associated with an increased DCD risk in a dose-response manner. Application of the WHO anemia criteria in men may miss patients with mild anemia that places them at DCD risk. Further research should look at anemia as a cause of reversible dementia. © 2022 The Author(s).

Avraham Weiss and Yichayaou Beloosesky equally contributed to the study initiation, data acquisition, and paper drafting.
**Introduction**

Anemia has long been considered to be associated with dementia in elderly people [1–7]. However, several recent studies have yielded inconsistent or negative results [8–11]. Some studies point to a U-shape relationship between hemoglobin (HGB) levels and risk of dementia [12]. Furthermore, the population groups investigated were not homogenous, with some studies, including individuals below what is classically considered the elderly, and the duration of follow-up varied [4, 6, 10, 12–16]. Some studies have alluded to the possibility that early identification and treatment of anemia in the elderly may have a protective or inhibitory effect against the development of dementia [6, 17] but there is as yet not enough supportive evidence.

The aim of the present study was to examine the potential association of anemia of all kinds with dementia and cognitive decline (DCD) risk in a large population of community-dwelling elderly subjects followed for 10 years. We hypothesize that such an association may be found among this study population.

**Materials and Methods**

Clalit Health Services (CHS) is the largest health maintenance organization in Israel with nearly 5 million members nationwide. The CHS database is a comprehensive state-of-the-art computerized data warehouse wherein data are aggregated by continuous real-time input from physicians and health service providers, including medical diagnoses, laboratory test results, and medications dispensed. Data can be queried to the level of an individual member.

For the present study, a historical prospective registry-based design was used. In this study, we looked at participants without DCD in the beginning of follow-up and prospectively measured the risk for the development of DCD. Data were derived from the database of the Dan-Petach Tikva District branch of CHS in central Israel covering a population of 51,512 community-dwelling subjects aged 65–124 years. Those for whom HGB levels were available at the start of the study in 2002 and who were dementia-free prior to that point were eligible for the study. “Baseline” serum HGB levels, upon entry to the study – 2002, were used. These levels reflect the community values that are not of an acute hospital stay. Subjects were followed to 2012 for the diagnosis of DCD as recorded in the medical records.

The diagnoses of DCD have been taken from the registry. These diagnoses are based on geriatrician’s/neurologist’s/psychiatrist’s evaluations. These diagnoses are based on MMSE tests and others (Clock Drawing test, MoCA test, Brain imaging, i.e., CT scan or MRI) [18]. Anemia of all kinds was defined in two ways: (a) according to HGB levels – according to the CHS, as HGB <14 g/dL for men and <12 g/dL for women, and according to the World Health Organization (WHO), as <13 g/dL HGB for men and <12 g/dL for women and (b) as retrieved from the diagnoses in the data registry [19, 20]. Baseline serum HGB levels (upon entry to the study) were categorized as follows: for men only, 13–14 g/dL or the difference between the lower limit of normal HGB level between CHS and the WHO; mild anemia, 11–13 g/dL for men, 11–12 g/dL for women; moderate anemia, 8–10.9 g/dL for men and women; and severe anemia, <8 g/dL for men and women.

The CHS database was queried for demographic data (age, sex) and conventional risk factors found to have a significant association with dementia in previous studies, namely, low socioeconomic status, hypertension, smoking status, diabetes mellitus, obesity, dyslipidemia, thyroid disorders, depression, Parkinson’s disease, and chronic renal failure. Serum albumin and alanine aminotransferase levels were also recorded as surrogate markers for nutritional status [21]. Low serum albumin level is also known to be associated with cognitive impairment [22].

**Statistical Methods**

Data are presented as mean and standard deviation for continuous variables and as frequency and percentage for categorical variables. Independent *t* test and *χ*² test were used to compare subjects with and without DCD and subjects with and without anemia, for baseline characteristics, associated diseases, and laboratory test results. Independent *t* test and Mann-Whitney nonparametric test were used to compare patients with and without anemia for time to DCD. Quartiles are presented in a box-plot graph.

Subjects were followed to the occurrence of DCD or death or the end of follow-up. Time to DCD was calculated from study onset (01/2003) to study end (12/2012), to DCD occurrence, or to death.

Conventional risk factors found to have a significant association with DCD were entered into a multivariate analysis using a Cox regression model for time to DCD. Anemia was introduced into the model as a dichotomous variable (diagnosed anemia), a categorical variable (dose-response), and a continuous variable (HGB level). Cumulative event-free curves were formulated to demonstrate the difference in adjusted risk of DCD between categories of HGB level. We further analyzed the association of HGB level with DCD risk by using the multivariate logistic regression model adjusted by all relevant covariates.

We also performed a competing risk analysis for all-cause mortality. In this competing risk model, we have found 11,442 participants who died from any cause.

Data were analyzed with SPSS software, version 25.0. (SPSS Inc., Chicago, IL, USA). The significance level was set at 0.05.

**Results**

Of the 51,512 community-dwelling subjects aged 65 years or more registered in the CHS database, 14,561 were excluded because they were diagnosed with dementia before the start of the study (January 1, 2002, *n* = 2,233) or they were missing HGB values in 2002 (*n* = 12,328). The final study population consisted of 36,951 subjects aged 65–113 years. Figure 1 depicts the selection process.
During the 10-year study period (2003–2012), DCD was diagnosed in 7,180 subjects (19.4%). Table 1 compares background parameters between patients with and without DCD. The DCD group had a higher mean age, a greater proportion of women and of unmarried subjects, and higher rates of hypertension, diabetes mellitus, atrial fibrillation, depression, cerebrovascular accident, and Parkinson’s disease. They had lower mean levels of serum albumin and alanine aminotransferase and a higher rate of anemia according to the criteria of both CHS and the WHO. Table 2 compares baseline characteristics between participants with and without anemia. Participants with anemia had a higher mean age, a greater proportion of men, higher rates of lower socioeconomic state, diabetes mellitus, hypertension, CRF, malignancy, cerebrovascular events, and Parkinson’s disease.

On unadjusted Cox regression analysis, after 10 years of follow-up, the hazard ratio (HR) for DCD was 1.47 (95% CI: 1.39–1.55) when the CHS criteria for anemia were used and 1.66 (95% CI: 1.66–1.55) when the WHO criteria were used. The time to development of dementia was 1,527 days in the subjects with anemia compared to 2,146 days in the subjects without anemia (Fig. 2).

On multivariate Cox regression analysis, after adjusting for age and sex, the HR for the development of DCD overtime was 1.45 (95% CI: 1.37–1.54) when the CHS criteria for anemia were used and 1.51 (95% CI: 1.41–1.61) when the WHO criteria for anemia were used. When more parameters were entered into the model the association remained strong and significant: HR 1.31 (95% CI: 1.24–1.39) using the CHS criteria (Table 3), and 1.39 (95% CI: 1.30–1.49) using the WHO criteria. Specifically, for HGB level 13–14 g/dL the adjusted HR was 1.20 (1.09–1.32), p < 0.001. There was a similar trend of DCD risk among men and women: for men the HR for DCD risk was 1.28 (CI: 1.17–1.39, p < 0.001) and for women: HR = 1.40 (CI: 1.29–1.52, p < 0.001).

A separate analysis was performed of the 27,184 subjects (73.6%) for whom both HGB and albumin values were available in 2002. The results showed that DCD risk was inversely associated with albumin level (HR = 0.57, 95% CI: 0.52–0.62) and, as found for the whole registry,
Table 1. Baseline characteristics of total study group by DCD

|                          | Total study group (n = 36,951) | DCD (n = 7,180) | No DCD (n = 29,771) | p value |
|--------------------------|--------------------------------|-----------------|---------------------|---------|
| Age, mean ± SD, years    | 83±6.3                         | 85.6±6.0        | 82.6±6.2            | <0.001  |
| Sex – male               | 14,948 (40.5)                  | 2,554 (36)      | 12,394 (42)         | <0.001  |
| Marital status – unmarried| 24,625 (67)                    | 5,439 (76)      | 19,186 (64)         | <0.001  |
| Smoking                  | 3,550 (9.6)                    | 560 (7.8)       | 2,990 (10.0)        | <0.001  |
| Obesity                  | 6,110 (16.5)                   | 1,004 (14)      | 5,106 (17)          | <0.001  |
| Low socioeconomic status | 7,651 (21)                     | 1,419 (21)      | 6,232 (21)          | 0.201   |
| Diabetes mellitus        | 6,203 (17)                     | 1,360 (19)      | 4,843 (16)          | <0.001  |
| Hypertension             | 7,791 (21)                     | 1,630 (23)      | 6,161 (21)          | <0.001  |
| Atrial fibrillation/flutter| 5,706 (15)                     | 1,219 (17)      | 4,487 (15)          | <0.001  |
| Hyperlipidemia           | 26,571 (72)                    | 4,943 (69)      | 21,628 (73)         | <0.001  |
| Depression               | 5,817 (16)                     | 1,889 (26)      | 3,928 (13)          | <0.001  |
| Hypothyroidism/hyperthyroidism | 859 (2.3)               | 189 (2.6)       | 670 (2.3)           | 0.054   |
| Chronic renal failure    | 896 (2.4)                      | 144 (2.0)       | 752 (2.5)           | 0.010   |
| Malignancy               | 804 (2.2)                      | 112 (1.69)      | 692 (2.3)           | <0.001  |
| Cerebrovascular accident | 3,879 (10.5)                   | 983 (14)        | 2,896 (10)          | <0.001  |
| Parkinson disease        | 2,957 (8)                      | 394 (5.5)       | 846 (2.8)           | <0.001  |
| ALT, mean±SD, IU/L       | 19.6±50.8                      | 18.4±27.6       | 19.8±55             | 0.041   |
| Albumin, mean ± SD, g/dL | 3.89±0.36                      | 3.86±0.35       | 3.89±0.36           | <0.001  |
| Anemia, CHS, Hb          | 7,904 (21)                     | 1,601 (22)      | 6,303 (21)          | 0.037   |
| Anemia, WHO, Hb          | 5,198 (14)                     | 1,083 (15)      | 4,115 (14)          | 0.006   |
| No anemia, Hb            | 29,453 (80)                    | 5,654 (79)      | 23,799 (80)         | <0.001  |
| Δ13–14 g/dL              | 2,845 (7.7)                    | 543 (7.6)       | 2,302 (7.7)         | <0.001  |
| Mild anemia              | 3,729 (10.1)                   | 803 (11.2)      | 2,926 (9.8)         | <0.001  |
| Moderate anemia          | 914 (2.5)                      | 180 (2.5)       | 734 (2.5)           | 0.007   |
| Severe anemia            | 10 (0.01)                      | 0               | 10                  |         |

Values are given as n (%) unless otherwise stated. ALT, alanine aminotransferase.

Table 2. Baseline characteristics of total study group by anemia

|                          | Total study group (n = 36,951) | Anemia (n = 7,904) | No anemia (n = 29,047) | p value |
|--------------------------|--------------------------------|-------------------|------------------------|---------|
| Age, mean±SD, years      | 83±6.3                         | 83.9±6.99         | 82.9±6.09              | <0.001  |
| Sex, male                | 14,948 (40.5)                  | 5,101 (64.5)      | 9,847 (33.9)           | <0.001  |
| Marital status, unmarried | 24,625 (67)                    | 5,288 (66.9)      | 19,337 (66.6)          | 0.580   |
| Smoking                  | 3,550 (9.6)                    | 755 (9.6)         | 2,795 (9.6)            | 0.851   |
| Obesity                  | 6,110 (16.5)                   | 947 (12.0)        | 5,163 (17.8)           | <0.001  |
| Low socioeconomic status | 7,651 (21)                     | 1,825 (23.6)      | 5,826 (20.6)           | <0.001  |
| Diabetes mellitus        | 6,203 (17)                     | 1,816 (23.0)      | 4,387 (15.1)           | <0.001  |
| Hypertension             | 7,791 (21)                     | 1,761 (22.3)      | 6,030 (20.8)           | 0.003   |
| Atrial fibrillation/flutter | 5,706 (15)                     | 1,139 (14.4)      | 4,567 (15.7)           | 0.004   |
| Hyperlipidemia           | 26,571 (72)                    | 4,794 (60.7)      | 21,777 (75.0)          | <0.001  |
| Depression               | 5,817 (16)                     | 1,026 (13.0)      | 4,791 (16.5)           | <0.001  |
| Hypo/hyperthyroidism     | 859 (2.3)                      | 152 (1.9)         | 707 (2.4)              | 0.008   |
| Chronic renal failure    | 896 (2.4)                      | 467 (5.9)         | 429 (1.5)              | <0.001  |
| Malignancy               | 804 (2.2)                      | 343 (4.3)         | 461 (1.6)              | <0.001  |
| Cerebrovascular accident | 3,879 (10.5)                   | 1,195 (15.1)      | 2,684 (9.2)            | <0.001  |
| Parkinson’s disease      | 2,957 (8)                      | 344 (4.4)         | 896 (3.1)              | <0.001  |
| ALT, mean±SD, IU/L       | 19.6±50.8                      | 19.7±93.6         | 19.4±24.5              | 0.821   |
| Albumin, mean±SD, g/dL   | 3.89±0.36                      | 3.87±0.42         | 4.04±0.33              | <0.001  |

Values are given as n (%) unless otherwise stated. CHS, Clalit Health Services; WHO, World Health Organization; ALT, alanine aminotransferase.
directly associated with anemia (HR = 1.21, 95% CI: 1.12–1.29).

Analysis by the severity of anemia yielded a dose-response pattern. The more severe the anemia, the greater the risk of DCD developing during the 10-year follow-up period. The small number of subjects with severe anemia precluded a separate analysis of its impact on the development of DCD. Therefore, subjects were divided into 2 groups: mild anemia (HGB 11–13 g/dL men, 11–12 g/dL women) and moderate-severe anemia (HGB ≤8–10.9 g/dL). The results were as follows: HGB 13–14 g/dL (men only), HR = 1.20 (95% CI: 1.09–1.32); mild anemia, HR = 1.38 (95% CI: 1.28–1.49); moderate-severe anemia, HR = 1.64 (CI: 1.41–1.90) (Fig. 3). When HGB was analyzed as a continuous variable, every decrease in 1 standard deviation of HGB (1.4 g/dL) increased the risk of DCD development by 15% (HR = 1.15 [95% CI: 1.09–1.21]).

We have further analyzed our data using all-cause mortality as a competing risk for DCD. Anemia has still emerged as a risk factor for DCD, but the associated risk has been weakened, Table 4.

### Discussion/Conclusion

This study examined the risk of development of DCD over 10 years’ study (mean follow-up to DCD appearance: 7.4 ± 3.3 years) in a large community-dwelling elderly population with and without anemia. On unadjusted analysis, the risk was found to be considerably higher for subjects with anemia (47% using the CHS criteria, 66% using the WHO criteria). The risk and the risk difference were slightly lower but still significant on multivariate Cox regression analysis taking background diseases into account. Further support was provided by a sensitivity analysis exclusively of subjects for whom we also had albumin data at the beginning of the study. DCD developed 1.5 years earlier in the subjects with than without anemia, and the more severe the anemia, the higher

### Table 3. Risk factors for DCD (multivariate analysis Cox model)

| Risk Factor                  | HR   | 95% CI     | p value |
|------------------------------|------|------------|---------|
| Age                          | 1.05 | 1.05–1.06  | <0.001  |
| Male sex                     | 0.95 | 0.90–1.00  | 0.069   |
| Unmarried                    | 1.61 | 1.51–1.71  | <0.001  |
| Smoking                      | 0.90 | 0.82–0.98  | 0.015   |
| Obesity                      | 0.77 | 0.71–0.81  | <0.001  |
| Diabetes mellitus            | 1.47 | 1.39–1.56  | <0.001  |
| Hypertension                 | 1.07 | 1.01–1.13  | 0.020   |
| Atrial fibrillation/flutter  | 0.90 | 0.84–0.95  | <0.001  |
| Hyperlipidemia               | 0.62 | 0.59–0.66  | <0.001  |
| Depression                   | 1.65 | 1.57–1.74  | <0.001  |
| Hypothyroidism/hyperthyroidism| 1.00 | 0.86–1.16  | 0.998   |
| Chronic renal failure        | 1.08 | 0.91–1.27  | 0.384   |
| Malignancy                   | 1.05 | 0.87–1.27  | 0.612   |
| Cerebrovascular accident     | 1.68 | 1.57–1.80  | <0.001  |
| Parkinson's disease          | 1.97 | 1.78–2.18  | <0.001  |
| Anemia*                      | 1.31 | 1.24–1.39  | <0.001  |

CHS, Clalit Health Services, where study was performed. * Anemia according to CHS.
the HR for the development of DCD. This study is the first in Israel to show a direct association between anemia and DCD. In addition, the findings suggest that if the WHO threshold for anemia is used (13–14 g/dL), a significant proportion of elderly people at risk of DCD might be missed. This study was prompted by the considerable inconsistency in the literature regarding the association between anemia at baseline and the development of dementia during various periods of follow-up [2, 23].

Since 1997, an association between anemia and Alzheimer’s dementia was reported [2]. Like in our study, the association remained significant although somewhat weaker when various parameters were entered into the multivariate model in a prospective study recently published and others [4, 6, 13]. Another study [14] showing similar findings to ours also found a dose-response pattern between the level of anemia and risk of dementia that was statistically significant only in severe anemia. In the present study, both the adjusted risk association between anemia and DCD over time and the dose-response relationship were more significant.

The effect of high HGB levels on cognitive decline is controversial as well. There are studies that showed [10, 12] that both high and low HGB concentrations were associated with lower cognitive test scores. Some [12], observed a U-shaped association between HGB level and dementia, such that both low and high HGB levels were associated with increased dementia risk. These findings contrast with the present study wherein an inverse association was found between high levels of HGB with DCD risk. The difference might be at least partly explained by the larger size of our study population, their older age, and the higher proportion of patients in whom dementia developed during study follow-up (19.4% compared to 12.3% in the Rotterdam study) [10].

Contrary results to ours have also been reported by others [8–11]. Myint et al. [11] failed to find any association of anemia with cognitive impairment and delirium.

### Table 4. Risk factors for dementia (multivariate analysis Cox model with all-cause mortality as a competing risk)

| Risk Factor                  | HR    | 95% CI          | p value |
|------------------------------|-------|-----------------|---------|
| Age                          | 1.058 | 1.054–1.062     | <0.001  |
| Male sex                     | 0.910 | 0.860–0.963     | 0.001   |
| Unmarried                    | 1.300 | 1.222–1.383     | <0.001  |
| Smoking                      | 0.936 | 0.855–1.024     | 0.150   |
| Obesity                      | 0.841 | 0.784–0.903     | <0.001  |
| Diabetes mellitus            | 1.289 | 1.210–1.373     | <0.001  |
| Hypertension                 | 1.058 | 0.998–1.121     | 0.057   |
| Atrial fibrillation/flutter  | 1.011 | 0.948–1.078     | 0.743   |
| Hyperlipidemia               | 0.877 | 0.830–0.926     | <0.001  |
| Depression                   | 1.913 | 1.810–2.021     | <0.001  |
| Hypothyroidism/hyperthyroidism | 1.051  | 0.905–1.221    | 0.513   |
| Chronic renal failure        | 0.788 | 0.660–0.940     | 0.008   |
| Malignancy                   | 0.812 | 0.668–0.987     | 0.037   |
| Cerebrovascular accident     | 1.394 | 1.296–1.500     | <0.001  |
| Parkinson disease            | 1.619 | 1.450–1.808     | <0.001  |
| Anemia                       | 1.060 | 0.996–1.128     | 0.0690  |

### Fig. 3. Differential effects of the levels of anemia on development of DCD.
In the present study, the association of anemia with DCD was observed in both men and women. Others had different findings. In the PRO.V.A study [16], it was found that the potential value of a low HGB concentration to predict cognitive impairment was stronger in men than women. By contrast, Chang et al. [15] found that only women with dementia had a higher prevalence of prior iron deficiency anemia than women without dementia.

The range of normal HGB in men is 14–18 g/dL according to the CHS and <13 g/dL according to the WHO. In the present study, the lower HR for DCD using the CHS criteria for anemia compared to the WHO criteria suggests that a change in the WHO definition may be warranted. It is noteworthy that 543 new cases of DCD fell within the Δ13–14 g/dL in HGB level, accounting for 7.6% of the DCD diagnoses in the whole registry and 21% of the DCD diagnoses in men. In recent years, several experts have challenged the current values of low HGB concentration and revised anemia definition. In fact, they call for further investigation of this issue [24].

The mechanisms that may explain the association of anemia with DCD are complex and may include deprivation of oxygen delivery to the brain; thus impairing brain metabolism in anemic patients; increased blood flow thus delivering more uremic toxins to brain cells in patients with chronic kidney disease (CKD) and anemia [3]; Anemia might also be the result of other disease states like CKD or iron deficiency. These in turn may lead to oxidative stress to the brain cells enhancing brain aging [1, 13]. There are other pathways as well: anemia may lead to depression, a known risk factor for dementia. Fatigue is another consequence of anemia which may lead to physical inactivity with an increased risk for dementia [24]. Anemia may render the brain more vulnerable and more susceptible to postoperative delirium [25]. Anemia may challenge the aging brain vasculature and the brain neurons as changes that occur in cerebral blood vessels, as well as in the neural cells themselves, appear to result in reduced energy availability to neurons.

Anemia may aggravate Parkinson’s disease risk [26, 27] and the risk of stroke [28]. These diseases are known to be associated with higher risk of DCD development [29, 30].

Lately the new concept of “inflammaging” has evolved. This phenomenon connects inflammaging with many disease states – multimorbidity, including diabetes mellitus, CKD, anemia, depression, and dementia, all of which involve inflammaging as an important risk factor [31]. According to this concept anemia in elderly people may adversely affect their more susceptible brains due to inflammaging.

Obesity, smoking, and atrial fibrillation are known to be harmful to the elderly health. These parameters were found to be negatively associated with the risk of DCD development. We do not have satisfactory explanations for these associations. However, our results are in accordance with the literature. Obesity in some studies is negatively associated with dementia [32]. Smoking had been found in some early studies as negatively associated with dementia [33]. Atrial fibrillation in a few studies was not found to have direct association with dementia [34, 35].

This study is limited by its design being registry-based one, which has known inherent weaknesses. However, the study population was relatively large, and many of the findings were similar to other smaller prospective studies. We believe that the diagnoses of Cognitive decline and of Dementia usually express similar disease process and we addressed both as DCD.

Although cognitive test results in our database were lacking and the diagnosis of DCD was based on the electronic medical records, the methodology applied here has also been reported by others [13]. The diagnoses of DCD in our study are based on a specialist evaluation, and as stated above, according to appropriate cognitive and brain imaging tests. In addition, the percentage of the newly diagnosed cases of DCD during the study period was similar to other reports, indirectly supporting case ascertainment in this study registry.

We used baseline (upon entry to the study) serum Hb levels as reference values. We only took a “snapshot” of a certain point in time and from that point onward we look at DCD risk – a historical-prospective study. Most of the studies about the association between dementia and anemia, both prospective and retrospective studies, are based on a single HGB value at baseline [4, 6, 14, 16].

A separate analysis was performed of nearly 74% for whom both HGB and albumin values were available in 2002. The results showed that DCD risk was inversely associated with albumin level and, as found for the whole registry, directly associated with anemia. Even though these values of HGB and albumin are based on just a “snapshot,” upon entry to the study, it further strengthens the validity of our methods of analysis.

Although anemia per se is a risk factor for DCD as found by others and by us another limitation is that we included all kinds of anemia in the study, being aware to different mechanisms and therefore different approach to patients with different kinds of anemia. Other studies also did not relate to the type of anemia in their analysis [12,
Finally, upon applying the competing risk model, the effect of anemia on DCD risk among participants with anemia in comparison to participants without anemia has been somewhat weakened but with similar trend.

The strengths of our study were the large study sample, the older age of the subjects, long follow-up period, and the sensitivity analysis, which has not been previously reported. The latter further emphasized the association of anemia and DCD among elderly people and has implications for resolving the inconsistency in the literature. Finally, we showed that if the WHO criteria for anemia are used, some patients with anemia-related DCD may be missed.

Raising awareness among the medical community in general and geriatricians in particular of the strong association of anemia with the development of DCD over time may lead to efforts to look for early signs of DCD even at mild anemia. It should also encourage researchers to determine if early treatment of anemia might decrease the occurrence of DCD \[6, 17\] in which case anemia-associated DCD, at least in its early stages, could be considered a reversible dementia \[24\].

In conclusion, the 10-year study of a large sample of community-dwelling elderly subjects in Israel showed that anemia may be associated with an increased risk of DCD development and of early DCD development in a dose-response manner. Application of the current WHO criteria for anemia, especially in men, may cause clinicians to miss patients with a mild anemic state that places them at risk of DCD.

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**Statement of Ethics**

Since the study was based on registry, no informed consent was needed. The institute that waived the need for written informed consent is the Community Institutional Review Board of Dan District, Petach-Tikva; approval number: 0007-12-COM.

**Conflict of Interest Statement**

There are no conflicts of interest.

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**Author Contributions**

Conceptualization: A.W. and Y.B.; methodology: H. S.-W. and R.G.-B.; software: J.M. and E.S.; validation: Y.L.-W., Y.L., and F.M.; formal analysis: N.K.-M.; data curation: D.B. and N.I.; writing – original draft preparation: A.W. and Y.B.; writing – review and editing: H.S.-W. and R.G.-B.; all authors have read and agreed to the published version of the manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in the article. Further inquiries can be directed to the correspondence author.
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