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Vitamin B_{12} in different age and gender groups of effluent subjects and its relationship with depression: a population-based study

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Abstract

Depression is a usual outcome of different chronic diseases and causes irreversible damage by intensifying the complications associated with diseases. Numerous scientific evidences have ratified the inverse association between vitamin B_{12} and folate supplementation and depression. The relationship of vitamin B_{12} and folate with the age, gender was assessed in a population-based research study conducted in effluent subjects of Islamabad. Furthermore, the effect of vitamin B_{12} on the depression symptoms was also examined in the participating subjects. During the study the serum vitamin B_{12} and folate concentrations of 395 subjects, aged between 1 to 84 years, were also evaluated. The symptoms of depression were analyzed through Geriatric Depression Scale (GDS) and divided into 3 categories i.e. no, mild and severe depression. The blood hematology exhibited 178 subjects with depressive vitamin B_{12} serum levels. The deficiency of vitamin B_{12} was a sure sign of the existence of depressive disorders. The results of serum vitamin B_{12} deficiency were categorized for age, gender, and disorder. The female patients were found more vulnerable to depression related vitamin B_{12} deficiency. Similarly, aging also revealed substantial effect on the vitamin B_{12} deficiency i.e the older, the lesser vitamin B_{12} and more depression and vice versa. The depressive disorders were momentously reduced by administering vitamin B_{12} in the depressed subjects. The possible mechanistic cascades ratifying the relation between vitamin B_{12} deficiency depressions need to be explored to reveal other potential health benefits of vitamin B_{12}.

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Introduction

The depression is a leading basis of disability all over the world (Prince *et al.*, 2007) with its occurrence range 8.8 to 18.3% in elder population (Copeland *et al.*, 1999). The prevalence of depression in older age people is related to various causes, but some evidences suggest that coronary heart diseases (CHD) risk factors and other related diseases are involved in depression outcomes (Alexopoulos *et al.*, 1997). Basically depression is metabolic disorder of central nervous system. Moreover, vitamin B_{12} and folate are observed to be helpful for different metabolic pathways in the human central nervous system (Chanarin *et al.*, 1989). The vitamin B_{12} deficiency is mainly due to intrinsic factor deficiency, and hypochlorhydria affects mainly older people (Baik *et al.*, 1993 and Clarke *et al.*, 2003 ;). The symptoms of vitamin B_{12} deficiency include: anemia, neuropathy, and neuropsychiatric disorders, but it more commonly leads to fatigue in older genders (England *et al.*, 1976; Tufail *et al.*, 2018). During the previous era it was said that the deficiency of vitamin B_{12} was rarely considered as a disease, as it was easy to diagnose because of the remarkable findings of megaloblastic anaemia but now it is recommended that vitamin B_{12} deficiency is very common and that its occurrence increases with age as more in older people than in young ones. According to scientific studies in past few decades it was supposed to affect 5 to 40% of the aged people (Baik *et al.*, 1993). Nevertheless, data about vitamin B_{12} related factors in unselected aged groups are limited and many earlier studies were based on small and choosy samples.

It was further assessed that the advanced levels of vitamin B_{12} deficiency never cause diagnostic problems, but its early identification is challenging owing to limitation in laboratory procedures and speculative symptoms (Bjorkegren *et al.*, 2003; Schneede and Ueland, 2005). Therefore, early diagnosis is imperative for preventing irreparable damage as its advancement may lead towards severe health problems. The general physicians feel exasperating in probing the aged subjects with unclear symptoms because idiosyncratic symptoms are commonly absent in early vitamin B12 deficiency (Bjorkegren *et al.*, 2003), so the concern should be to focus on persons with known risk factors including smoking, alcoholism and vegetarian diet (Schneede and Ueland, 2005)). Moreover, the gastrointestinal diseases and gastric acid (Gregg, 2002) may enhance the cobalamin malabsorption which leads to anaemia. The pernicious anaemia is also considered to relate with other autoimmune diseases (Toh *et al.*, 1997). From the previous discussion it is evident that the deficiency of vitamin B_{12} mainly occurs among elderly patients and investigated a lot in these subjects, but it is mostly not investigated in other age groups because the clinical manifestations are subtle. In the present study, the prevalence of vitamin B_{12} deficiency was investigated in a representative sample of the different aged and gender population from Islamabad with special reference to depression and vitamin B_{12} deficiency in order to find out if a specific risk group among the different age and gender segments can be identified for further expanded study of major population.

Methodology

Subjects

This study was conducted on different age and gender groups of 395 effluent subjects. It was a population based study in which the participating subjects were aged between 01 years to 88 years in the city of Islamabad who attended the Uppals Clinics, Islamabad for the baseline assessment and their serum analysis of vitamin B_{12} and folate. All the 395 subjects were registered for census purposes in clinic and were invited to take part in a health survey and serum analysis. Each participant in the study was questioned about the willingness to provide blood samples collected through phlebotomist. The subjects visited the clinic and had overnight fasting blood samples drawn.

Analysis of depressive symptoms

The participants were passed through screening process for depression symptoms during the interview conducted by Dr. Rizwan Uppal at Uppals Clinics, Islamabad. Depressive symptoms were measured

following the method explained by Yesavage *et al.* (1983) through Geriatric Depression Scale and results were categorized as: a) no depression b) mild depression and c) severe depression. The score range for this scaling is 0-30, in which with high score indicates high levels of depressive symptoms and vice versa. By using the general cutoff scores (23, 24), the participants were categorized viz. no depression (got score ≤ 9), mild depression (got score = 10-13), and severe depression (got score ≥ 14).

The written informed consent was obtained from participants after brief description of the whole study. The willing participants were subjected to further clinical study.

Blood samples and biochemical analysis

The blood samples were collected from the subjects in fasting state. And were shifted into ethylenediamine tetra-acetic acid (EDTA) tubes, centrifuged, for separation of serum and plasma and stored at 70°C within 2 hrs of sample collection. Serum samples were further subjected to biochemical analysis. Serum vitamin B_{12} levels and folate concentrations were analyzed by using an immunoassay method. Furthermore, vitamin deficiency was determined by using the cut-off values (described above) that matched to the normal ranges of the assays and are described in the previous reports (Penninx *et al.*, 2000).

Determination of vitamin B_{12} deficiency

The definition of vitamin B_{12} is mainly related to two classifications i.e. using a high and low cutoff, for the survival of a dose reaction relationship with this vitamin prevalence (Stabler *et al.*, 1999). The high cutoff B_{12} deficiency is presented for serum vitamin B_{12} level ≤ 258pmol/l whereas, a low cutoff value is presented for serum B_{12} level ≤ 271nmol/l. However, the folate deficiency is presented when the serum folate level is ≤ 1.4nmol/l.

Statistical analysis

The following variables were considered as confounders during this study: 1) vitamin B_{12}, 2) age and 3) gender. The descriptive statistics by using SPSS version 17 was used to analyze the associations of vitamin B_{12} deficiency with depressive disorders explained in depression levels generated from GDS. Furthermore, mean levels differences were evaluated through ANOVA. The results were interpreted with the help of graphical plots of frequency distribution and the mean comparison of gender was also tested through "t" statistics.

Results and discussion

The results for the frequency distribution for all the participants explained in Figs 1 and 2 shows that age of both male and female gender subjects was ranged between 20 and 80 years. The results of this population-based study presented in Figs 3 and 4 further shows that elderly persons and female subjects who had vitamin B_{12} deficiency were found to possess more depressive disorders.

Table 1. Different characteristics of subjects participated in the epidemiologic study of depression and levels of vitamin B_{12}.

Characteristics	No Depression (N=152)		Mild Depression (N=118)		Severe Depression (N=115)	
	Mean	SD	Mean	SD	Mean	SD
Age (Years)	46.64	3.75	45.97	4.45	49.05	3.25
	N	%	N	%	N	%
Education (≥12 years)	44	28.94	49.15	74.57	37	32.17
Annual Income (Pak Rupees)						
≤1,00000	24	15.19	25	21.86	64	55.65
1,00000-2,00000	75	49.34	63	53.38	29	25.22
≥2,00000	53	34.87	30	25.42	22	19.13
Use of vitamin preparations						
Vitamin B complex	36	23.68	20	16.95	13	11.30
Vitamin B12	17	11.18	14	11.86	5	0.04
Multivitamin	69	45.39	41	34.75	37	32.17
Never	30	19.74	43	36.44	60	52.17

[a] Depression status was determined with the Geriatric Depression Scale. No depression: score≤9; mild depression: score=10–13; severe depression: score≥14.

The results from Fig. 2 explain the fit line regression graph for the presence of vitamin B_{12} in both genders whereas the regression was particularly done for female subjects who showed more depressive symptoms. Furthermore, a non-significant relationship was observed in case of folate deficiency. The depression was not associated to folate deficiency. The possible factors might be due to physical comorbidity and cardiovascular risk factors in subjects with depression.

Table 2. Relationship of depression status[a] to serum levels of vitamin B_{12} and folate and their deficiencies in subjects.

Variables	No Depression (N=152)				Mild Depression (N=118)				Severe Depression (N=115)			
Serum levels of vitamins	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%
Vitamin B_{12}												
Level (pmol/l)	516	414			438	377			288	278		
Subjects with level ≤258			42	27			49	41			83	66
Subjects with level ≤148			15	9.8			20	17			44	35
Folate												
Level (nmol/l)	13.5	5.6			13.7	4.5			14.2	5.8		
Subjects with level ≤11.4			76	50			42	35.59			24	20.87
Rates of vitamin deficiencies												
Vitamin B_{12} deficiency			38	25			43	36.44			56	48.69
Folate deficiency			67	44.07			35	29.66			24	20.87

[a] Depression status was determined with the Geriatric Depression Scale. No depression: score≤9; mild depression: score=10–13; severe depression: score≥14.

The mean age of the study sample was 62.9 years. Among the 395 participants, 152 (38.48%) were found in category of no depression, 118 (29.87%) were in mild depression, and 125 (31.64%) were in severe depression. The results of demographic characteristics and disease status are presented in Table 1 that clearly indicated that the depressed subjects had less education compared to the non-depressed subjects. However, very few differences were observed with respect to income and use of vitamin preparations. When high cutoff i.e., serum vitamin B_{12} level less than 258 pmol/liter was considered for the prevalence of vitamin B_{12} deficiency the deficiency was found in 7.1% of the participants (Table 2). The results of table 2 also show the serum vitamin and folate concentrations and it was observed that the vitamin deficiency was more prevalent in depressed subjects. It is further elucidated in Table 2 that the subjects with lower vitamin B_{12} levels possessed mild and severe depression symptoms as compared to the subjects who had higher and normal vitamin level with no depression symptoms. It was further observed that about 40% of the subjects with depression symptoms scored below the vitamin B_{12} cutoff i.e. 258 pmol/liter, furthermore this value was significantly higher than the 31.6% that was found in the subjects with no depression. The significant vitamin B_{12} deficiency was observed among the subjects with severe depression and mild depression compared to the subjects with no depression (Table 2). The Table 2 also indicates that the subjects with mild and severe depression found to possess lower vitamin B_{12} levels than the subjects with no depression. However, the folate deficiency was not linked with depression status as observed in the present study. From the results of the study we found that the subjects with higher rates of vitamin B_{12} deficiency tend to show a risk of depression and moreover that risk was double the risk found in the subjects without vitamin B_{12} deficiency. The higher risk of vitamin deficiency was present for severe depression but not for mild depression in this study. However, the folate deficiency was found to have no link with depression.

The subjects with depressive symptoms were more likely to be female. Among 215 subjects, about 132

were with depressive symptoms (Table1). When vitamin B_{12} was assessed it was found that subjects with vitamin B_{12} deficiency were nearly 70% more likely to have a depressive disorder compared to the non-deficient subjects (Table 1). It was observed from present study and further ratified by the previous studies that the prevalence of cardiovascular disease excelled the deficiency of vitamin and consequently the depression symptoms.

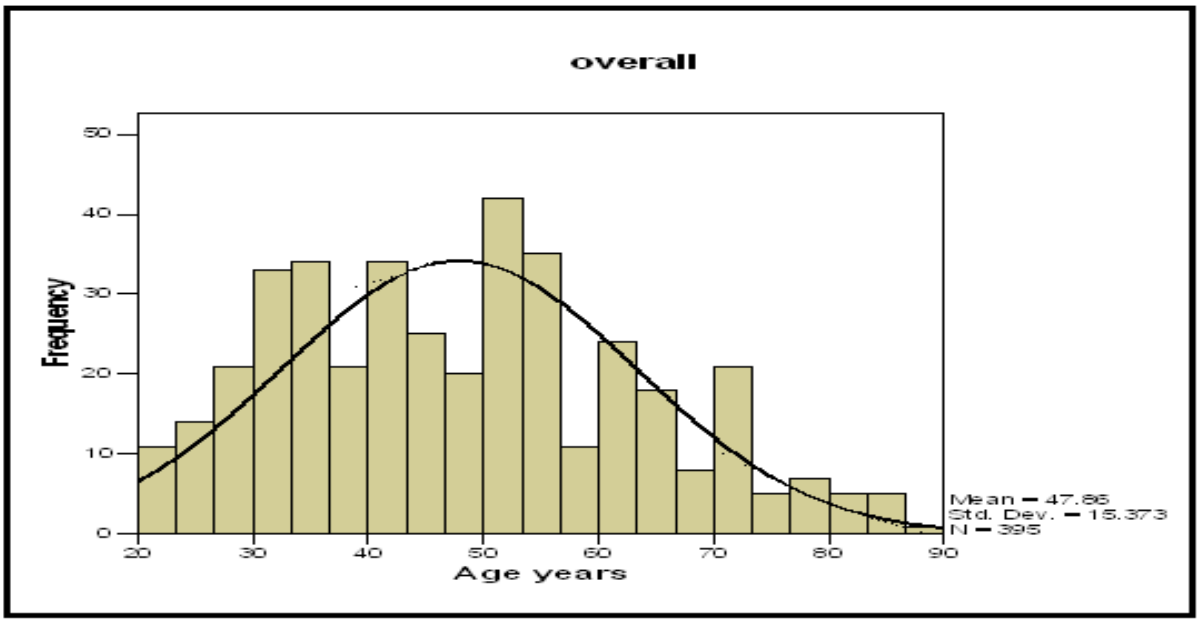

Fig. 1. Frequency distribution of male and female subjects of different age groups.

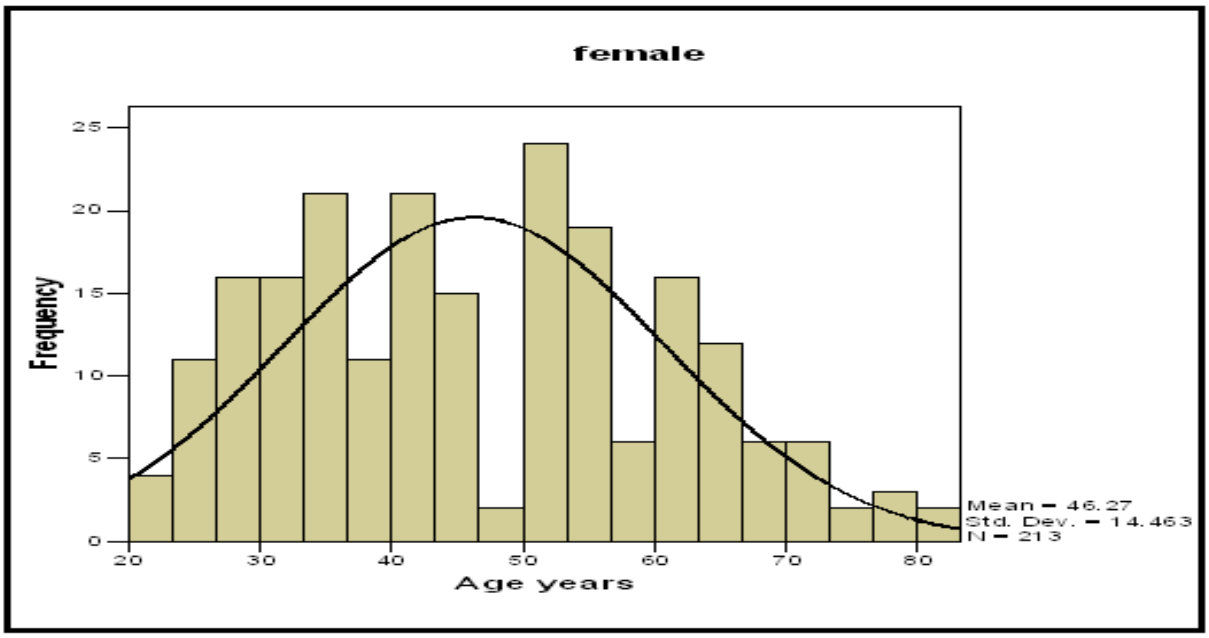

Fig. 2. Frequency distribution of female subjects of different age groups.

During the study relating to the gender groups of male and female it was clearly observed that age and gender possessed a clear link with the vitamin deficiency and consequently the depression symptoms. However, a non-significant effect of folate deficiency was evident from the present study and it showed least response towards depression in the subjects. The outcomes of the current study is of view that sufficient levels of vitamin B_{12} and folate are necessary to maintain the normal neurological system

activity that is otherwise adversely effected on account of vitamin B_{12} deficiency resulting in poor nervous co-ordination ultimately leading to depression. It is known that two enzymes promote the occurrence of vitamin B12 deficiency which are: 1) L-methylmalonyl-CoA mutase and 2) methionine synthase.

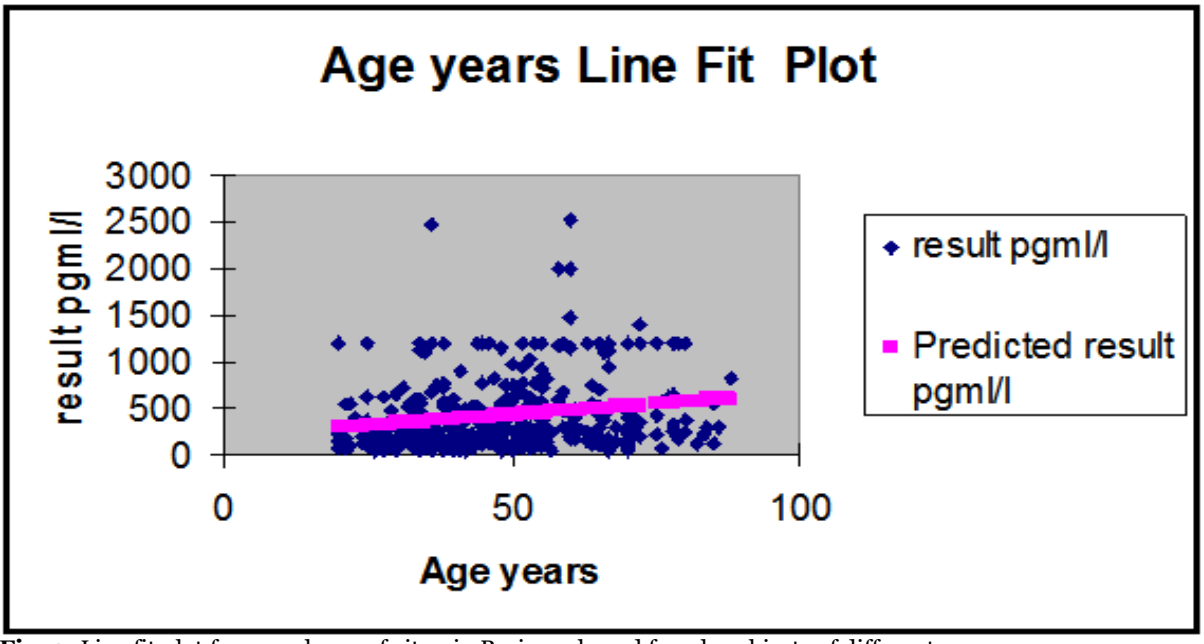

Fig. 3. Line fit plot for prevalence of vitamin B_{12} in male and female subjects of different age groups.

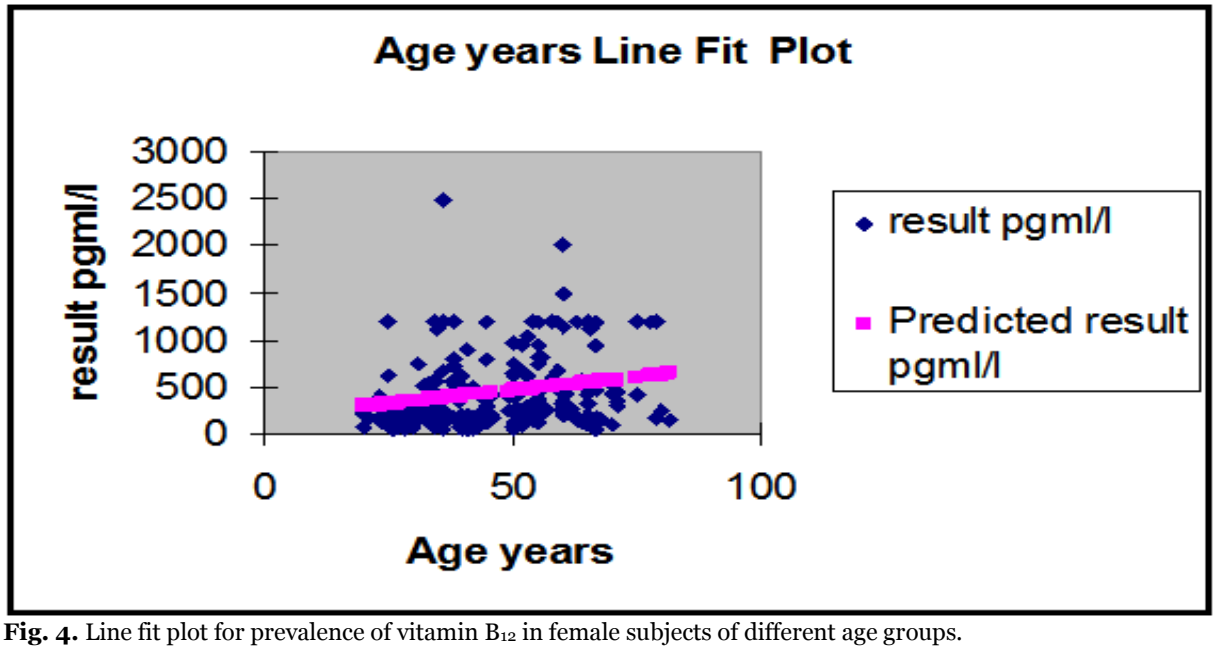

Fig. 4. Line fit plot for prevalence of vitamin B_{12} in female subjects of different age groups.

These enzymes were found to be associated with vitamin B_{12} which proved that deficiency of vitamin B_{12} significantly decreases by the action of these two enzymes. Furthermore, it was reported that accumulation of methylmalonic acid and homocysteine, respectively are also involved in the prevalence of vitamin B_{12} deficiency. However, regarding the pathways of this compound different neurotoxic mechanisms were found to be involved that include: 1) a buildup of *S*-adenosylhomocysteine and 2) an increased metabolism of homocysteic acid. Both of these mechanisms ultimately lead to the

activation of *N*-Methyl-D-aspartate receptors (Parnetti *et al.*, 1997) that are sensitive regarding vitamin deficiency. Similarly, the production of *S*-adenosylmethionine is also associated with the level of vitamin B_{12}. This compound is a major methyl donor in different methylation reactions in brain and it has antidepressant function (Coppen *et al.*, 1989). Therefore, its resisted synthesis may cause depression. However, our findings encourage further research efforts in the area of neurological coordination with special reference to vitamin B_{12} deficiecy and depression. On the other hand, when the relationship of folate deficiency was evaluated for depression symptoms, it was clearly observed from the results that no or mild relationship was depicted from this study. The results of the present study are inconsistent with the findings from some (Tufail et. al. 2018) regarding the patients with psychiatric depression and it was observed that severity of depression was not correlated with folate deficiency. However, it was observed that depressed patients with folate in the deficient range had more severe depression than those with folate in the normal range (Carney *et al.*, 1990). The differences between the current study and previous findings may be due to the reason that previous studies utilized only serum folate levels for the diagnosis of folate deficiency whereas, the use of serum metabolites are the better way to confirm the actual level of this vitamin in serum. The findings of the present study are consistent with the results of Penninx *et al.* (2000), in which the authors reported their results about physically disabled women and described that disability was related to the vitamin B_{12} deficiency and furthermore the depressive disorder were twice in case of vitamin deficient women than those with normal level of this vitamin. Similarly, the authors also observed no association between folate and depression that is in line with the present study. It is further suggested from the findings of present study that the higher risks of depressive disorders in vitamin B_{12} deficient subjects may be due to the differences in cardiovascular factors and physical comorbidity which is variable among the participating subjects as mentioned in demographic parameters explained in table 1.

Conclusion

The present study confirmed that the vitamin B_{12} deficiency may be related to the depression in the elderly and female subjects but such condition was not significantly prevalent among the young and male subjects.

The outcomes of the present study may serve as a benchmark in the diagnosis of depression with special reference to vitamin B_{12} deficiency and should be disseminated among the clinicians and physicians as this will be helpful in screening out different subjects and finding the exact background of depression, a main cause of different physical and health problems. However, the present study was unable to find any direct relationship between folate concentration and depression in the participating groups.

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