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Association between Metformin, Vitamin B12 Supplements, and Vitamin B12 Deficiency in Type 2 Diabetic Adults: NHANES 1999-2006

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Abstract

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Context Metformin is currently recommended as the primary treatment for diabetes and pre-diabetes by the ADA. The association between metformin and vitamin B12 levels has been documented but knowledge regarding the attenuation of this relationship by vitamin B12 supplements is lacking. This information is especially important in older Americans who are at greater risk for both diabetes and vitamin B12 deficiency.

Objectives To describe the prevalence of metformin associated vitamin B12 deficiency among US adults over 50 with type 2 diabetes and how this relationship is potentially modified by vitamin B12 supplements.

Design, Setting, and Participants Analysis of the nationally representative NHANES surveys from 1999-2006 of US adults over 50 who were either type 2 diabetic or non-diabetic (n=1621,6851). Type 2 diabetics were defined as those who were clinically diagnosed over the age of 30 and did not start insulin within one year of diagnosis. Population prevalence calculations were weighted according to NHANES guidelines to represent the non-institutionalized US population over 50.

Main Outcome Measurements Serum B12 levels were classified as deficient at or below 148pmol/L and borderline from 148 to 221 pmol/L.

Results Vitamin B12 deficiency was present in 5.5% of diabetics on metformin and in 2.1% of diabetics not on metformin ($p<.05$). Borderline B12 deficiency was found in 12.8% of diabetics on metformin and in 6.1% of diabetics not on metformin ($p<.01$). A stratified analysis based on B12 supplement use indicated first, that taking B12 was protective against deficiency, and second, that for diabetics on metformin, a minimum of 100 μgs of B12 should be taken daily. Metformin use was significantly associated with serum B12 deficiency and borderline deficiency in a logistic model adjusted for age, race, sex, and antacid use by odds ratios of 2.73 (95% CI 1.20-6.18) and 2.20 (95% CI 1.22-3.99) respectively.

Conclusion Metformin use puts US adults over 50 at a greater risk for vitamin B12 deficiency. This risk is reduced by B12 supplement intake at levels of 100 micrograms per day or higher. Health care providers should be aware of this relationship and serum B12 levels should by monitored annually in diabetics taking metformin while the recommendation to take sufficient B12 supplements is made evident.

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BACKGROUND

Diabetes

Diabetes is a chronic disease of global significance characterized by hyperglycemia due to defects in insulin secretion, action, or both. There are three major forms: type 1, type2, and gestational. These three forms have been described extensively elsewhere, but in brief, type 1 is an auto-immune disorder, and is usually apparent at an early age. Gestational diabetes is associated specifically with glucose intolerance during pregnancy. Type 2 diabetes encompasses over 90% of diabetic cases [1] and currently affects an estimated 7.8% of the US population [2]. The prevalence of diagnosed diabetes is projected to increase by 50%, moving from an estimated 5.9% in 2007[2] to 8.9% in 2025 [3]. The risk of developing type 2 diabetes increases with age, weight and physical inactivity [1]. Trends in prevalence reveal the importance of age as a risk factor. In 2007, the estimated prevalence of diagnosed and undiagnosed diabetes in the US was 2.6% for adults 20-39 years of age, 10.8% for those 40-59, and 23.1% for those 60 and older [2].

Two methods of treatment and prevention for type 2 diabetes have been successfully tested in randomized control trials: lifestyle and medication. In their landmark study, the Diabetes Prevention Research Group found a reduced incidence in diabetes of 58% by lifestyle modification and 31% by metformin therapy [4]. The American Diabetes Association currently recommends lifestyle modification and metformin therapy as primary treatment approaches for type 2 diabetes [5].

Metformin

Metformin is an oral biguanide drug that was approved for the treatment of non-insulin dependent diabetes in the US in 1995 [6]. Metformin functions biologically by decreasing glucose production in the liver and decreasing intestinal absorption while increasing absorption elsewhere [7].

Its mechanism of action improves glucose tolerance and contributes to weight loss and is prescribed not only to prevent diabetes but also to treat. Data from NHANES 1999-2004 suggest that approximately 25% of type 2 diabetics take metformin [8].

The review of metformin as drug therapy was published in 1996, shortly after its release into the US market. In the review, authors Bailey and Turner acknowledged potential side effects to be gastrointestinal, a rare risk of lactic acidosis, and impaired absorption of vitamin B12 (and possibly folic acid) [9]. Since that study, and even before, many groups have reported case studies and epidemiologic research of metformin-associated anemia and/or vitamin B12 deficiency. These studies are summarized in Table 1.

Vitamin B12 Deficiency

Vitamin B12, also known as cobalamin, is an essential ingredient to the human body and its depletion is associated with several adverse health outcomes including anemia, peripheral neuropathy, cognitive decline, and depression [10]. Neuropathy is an exceptionally important consequence of B12 deficiency in diabetics as being diabetic alone puts patients at greater risk of peripheral neuropathy. Recognizing the correct source of the neuropathy is essential to determining the appropriate treatment.

Current recommendations call for a daily intake of 2.4μg of vitamin B12 [11]. Little over 50% of the actual dose of B12 is absorbed, and this absorption is dependent on the binding capacity of intrinsic factor [12]. In the US, approximately 6% of adults over 60 are B12 deficient and around 20% are borderline deficient [13]. The three main causes of low B12 levels are a lack of sufficient B12 in the diet, malabsorption, and pernicious anemia [14]. Pernicious anemia is an autoimmune disease which results in the inability to synthesize intrinsic factor, the enzyme required for B12 absorption in the ileum. The prevalence of undiagnosed pernicious anemia was estimated to be 1.9% among US adults over 60 with 2.7% in women and 1.4% in men [15].

ABSTRACT

Context Metformin is currently recommended as the primary treatment for diabetes and pre-diabetes by the ADA. The association between metformin and vitamin B12 levels has been documented but knowledge regarding the attenuation of this relationship by vitamin B12 supplements is lacking. This information is especially important in older Americans who are at greater risk for both diabetes and vitamin B12 deficiency.

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Conclusion Metformin use puts US adults over 50 at a greater risk for vitamin B12 deficiency. This risk is reduced by B12 supplement intake at levels of 100 micrograms per day or higher. Health care providers should be aware of this relationship and serum B12 levels should by monitored annually in diabetics taking metformin while the recommendation to take sufficient B12 supplements is made evident.

INTRODUCTION

Vitamin B12 deficiency is a relevant public health issue for American adults. It is related to several hematologic and neuropsychiatric health outcomes including anemia, peripheral neuropathy, depression and cognitive impairment [10]. Recent national data suggest that approximately 6% and 20% of adults over 60 are B12 deficient or depleted, respectively [13]. The main causes of this depletion in the US are poor dietary intake and malabsorption. In those without underlying malabsorption or other clinical mechanisms of reduced B12 absorption, taking B12 supplements reduces the risk of both B12 deficiency and depletion. In their analysis of NHANES III, Evatt et al found that supplement users over 50 years of age had an approximately 75% lower prevalence compared to non-users (1.5% vs. 5.9%, p=.001) [16]. Among diabetics especially, the drug metformin has been studied in its relation to lowered vitamin B12 levels. Adding to the importance of these issues is the current diabetes epidemic. With the lifetime risk of diabetes calculated to be approximately one in three [17] and metformin being prescribed as the primary intervention [18], acknowledging its effects on serum B12 levels merits sincere clinical attention.

The metformin related depletion of serum B12 has been documented in both observational studies and randomized control trials, beginning with the first efficacy trial. DeFronzo et al demonstrated that while metformin demonstrates superior control of cholesterol and lipid levels compared to sulfonylurea, it also specifically affects serum B12 levels while leaving folate levels intact. After 29 weeks on metformin, serum B12 levels were lowered by 22% compared to placebo, and 29% compared to glyburide therapy[19]. Other studies have documented the same effect, and the results are summarized in Table 1.

Research strongly suggests that a relationship exists between metformin use and vitamin B12 levels. Recommendations have been made to screen diabetics on metformin for serum B12 levels [20-

30] though to our knowledge this practice has not been implemented. In previous studies, vitamin B12 therapy was successfully used to correct the metformin induced decline in B12 [25, 29, 31-33]. However, the use of B12 supplements in the general type 2 diabetic population on metformin has not been examined. It was therefore the aim of the present study to use the nationally representative NHANES population to determine the prevalence of metformin-associated B12 deficiency among type 2 diabetics over the age of 50 and to explore how this relationship is potentially ameliorated by taking B12 supplements.

METHODS

Study Design

NHANES is a nationally representative health and nutrition survey of US children and adults conducted by the National Center for Health Statistics as part of the Centers for Disease Control and Prevention. Greater details have been described elsewhere, but in general NHANES is a complex sample survey with targeted oversampling of certain age and racial/ethnic groups [34]. All participants offered written informed consent and the survey protocol was approved by a human subjects review board.

Study Population and Variable Definitions

Our study used data from NHANES 1999-2006. We restricted our analysis to adults aged 50 and older for a total of 8,472 subjects. Among this subset, we categorized the older adults as being non-diabetic, type 2 diabetic, or type 1 diabetic. Type 1 diabetics were defined as those who were diagnosed with diabetes before the age of 30 and began insulin therapy within one year of diagnosis. They were removed from the final analysis. Type 2 diabetics were any other participants who confirmed receiving a physician's diagnosis (not including gestational diabetes). Among the rest of the population, adults who reported being borderline or pre-diabetic were removed. For our final analysis we used 1,621 type 2 diabetics and 6,851 non-diabetics.

Participants were asked about their age, sex, race/ethnicity, weight and height, supplement and prescription medication usage, and age at diagnosis of diabetes. Blood samples were used to determine serum folate, Vitamin B12, homocysteine, hematocrit, creatinine, and methylmalonic acid. MMA was not measured for NHANES 2005-2006 and was therefore removed from the final analysis due to missing data. Macrocytosis was defined as mean cell volume greater than 99 fL. Anemia was defined according to WHO guidelines as hemoglobin below 13g/dL for men and below 12g/dL for women [35].

Vitamin B12 deficiency was defined as serum levels below 148 pmol/L. Borderline B12 depletion was defined as serum B12 between 148 and 221 pmol/L. Normal levels were those over 221 pmol/L. For supplementation, participants were asked about their supplements and frequency taking them. This information was used to calculate average daily intake. Vitamin B12 supplement intake was thoroughly analyzed. We categorized the average amount taken per day as 0 micrograms, great then 0 through 6 mcgs, 6 through 25 mcgs, 25 through 100 mcgs, 100 through 500 mcgs, 500 through 1000 mcgs, and over 1000 mcgs based on dietary supplement type and average weekly intake.

In the prescription medicine questionnaire, participants were asked about their medications and length of time taking them. For type 2 diabetics specifically, we grouped them into those who currently take metformin (alone or in combination) versus those who do not currently take metformin.

In order to closely examine the biological and demographic characteristics of those participants who were B12 deficient or borderline deficient, we also visualized a line listing of the cases.

On a final note, we excluded participants with positive HIV antibody test results, pregnant women, and those with high creatinine levels (defined as greater than 1.7mg/dL for men and 1.5mg/dL for women).

Statistical Methods

All statistical analysis was performed in SAS version 9.2 (SAS Institute, Cary, North Carolina) and SUDAAN version 10.1 software (Research Triangle Park, North Carolina) according to NHANES guidelines for analysis. Appropriate sample weights and variances were applied to account for the complex sample survey design.

SAS survey procedures and SUDAAN proc descript were used to characterize means, geometric means, and proportions. Continuous variables were tested for significance using t-tests and categorical

variables were tested by the X^2 test. Logistic regression was performed in SUDAAN with a dichotomous outcome using proc rlogist (serum B12 <148pmol/L for deficient or 148-221 pmol/L for borderline). Risk factors for vitamin B12 deficiency were assessed that were identified in previous research and included metformin use, age, race/ethnicity, gender, the use of proton pump inhibitors, H2 blockers, antacids, and B12 supplements, alcohol use, current smoking, and length of time with diabetes [36] [37]. Alcohol use was defined as positive for those who reported having between 2 and 50 drinks over the past month. Cigarette smoking was defined as those who reported current smoking. These two variables, however, could not be include in the logistic model due to extreme proportions of missing responses (86% of diabetics missing response to smoking and 66% missing response to alcohol use).

NHANES 1999-2006 had a large enough type 2 diabetic (n=1621) and non-diabetic (n=6851) sample size to detect a 5% difference at 90% power and alpha of .05. The study was sufficiently powered at over 95% for the comparison of diabetics to non-diabetics and the within comparison of diabetics on metformin vs. those on other treatments.

RESULTS

The demographic and biological characteristics of the study populations are summarized in Tables 2-4. As displayed in Table 2, among diabetics, those taking metformin were younger, diagnosed with diabetes for a shorter amount of time, took insulin less frequently, had lower serum B12 levels, and had a higher prevalence of B12 deficiency and borderline deficiency ($p<.05$).

As a second comparison group, we examined the demographic and biological characteristics of the general over-50 non-diabetic population compared to diabetics taking metformin (Table 3). The weighted prevalence of vitamin B12 deficiency and borderline deficiency among non-diabetics was 3.3% and 11.4%, respectively. The prevalence was lower than in diabetics taking metformin, but the differences were not statistically significant. In Table 3, differences in body mass index, race, hemoglobin A1C%, hemoglobin, and anemia are most likely attributable to being diabetic. Disregarding these dissimilarities, diabetics on metformin were less likely to use supplements, had lower serum B12 levels and lower rates of macrocytosis ($p<.05$).

As a final comparison, we examined the characteristics of the non-diabetic population compared to diabetics not taking metformin (Table 4). Besides the predictable differences related to being diabetic, there were other dissimilarities between these two groups. More non-diabetics took supplements and thus consumed more B12 and folic acid ($p<.01$). Diabetics not taking metformin had higher homocysteine and serum folate levels ($p<.05$). Surprisingly, the diabetics also had better Vitamin B12 levels; fewer diabetics not taking metformin had B12 deficiency or borderline deficiency compared to the regular population ($p<.05$).

From 1999-2006, the weighted prevalence of B12 deficiency and borderline deficiency among the non-institutionalized US adult population over 50 was 3.3% and 9.4% for diabetics, and 3.3% and

11.4% for non-diabetics (p=.9314,.0134). B12 deficiency and borderline deficiency among diabetics taking metformin was 5.5% and 12.8%, respectively. The weighted prevalence among diabetics not taking metformin was nearly half as much, at 2.1% and 6.1%. These differences were statistically significant (p<.05). Among diabetics who were deficient, metformin use was attributable to 42% of cases.

General B12 supplement use reduced the prevalence of low B12 levels (<221 pmol/L) by approximately 60% in non-diabetics, 50% in diabetics not taking metformin, and 33% in diabetics taking metformin (Table 5). There appeared to be a dose-dependent relationship among all three groups. Among diabetics taking metformin, daily B12 intake of 6-12µgs reduced the prevalence by approximately 66.7% whereas low B12 levels weren't observed at daily intake levels of 100µgs or higher. These results are consistent with published research where metformin-induced B12 deficiency was recovered through B12 injections which are usually 1000 µgs [25, 29, 31, 33]. After stratifying on B12 supplement use among diabetics, those taking metformin had consistently higher rates of deficiency.

Among diabetics, metformin use was associated with B12 deficiency and borderline B12 deficiency after adjusting for age, race, sex, and antacid use by odds ratios of 2.73 (95% CI 1.20-6.18) and 2.20 (95% CI 1.22-3.99) (Table 6). B12 supplement use was protective against both deficiency and borderline deficiency among diabetics, but only significantly for borderline (OR .93, 95% CI .41-2.11; OR .47, 95% CI .25-.88). B12 supplement use was also protective in the non-diabetic population at odds ratios of .32 (95% CI .21-.48) and .30 (95% CI .24-.38) for deficiency and borderline deficiency, respectively. Antacid use was significantly associated with borderline deficiency among diabetics, but this effect was lost after controlling for metformin use (OR 2.26 95% CI .96-5.35).

In the diabetic population there were 40 observations with Vitamin B12 deficiency and 149 with borderline B12 deficiency (Tables 7-8). In the deficient group, there were several potential cases of

undiagnosed or untreated pernicious anemia. These cases had low B12 levels, elevated MMA levels (for those whose MMA was measured), and elevated homocysteine levels. The second observation, case 297, is clearly a missed case of pernicious anemia. This woman, aged 75, had serum B12 of 34 pmol/L, methylmalonic acid of 35 umol/L, had both anemia and macrocytosis, and she reported taking B12 supplements (although the daily amount was not available). This case represents an important part of the older US population with clear pernicious anemia that hasn't been treated by the medical institution.

DISCUSSION

The results of this analysis suggest three important findings. First, taking vitamin B12 supplements is consistently protective against both B12 deficiency and borderline deficiency. In patients where supplements aren't effective, diagnostic tests for pernicious anemia or other mechanisms of malabsorption should be performed. Second, there is a clear relationship between metformin and reduced serum B12 levels. This has been well documented in three recent randomized control trials, and the same effect was observed in this cross-sectional sample of the US population (Table 1) [20, 24, 38]. Third, based on our exploration of the individuals with low serum B12, there are US adults with either untreated or unrecognized vitamin B12 deficiency. Vitamin B12 deficiency is common and certainly needs attention. A clear example is the 75 year old woman with extremely low serum B12, extremely high methylmalonic acid and both anemia and macrocytosis (Table 7, case 297). This case implies that screening for both B12 deficiency and pernicious anemia is important in older US adults, especially diabetics. Low serum levels in general may or may not be harmful. Undiagnosed or untreated pernicious anemia is, and these cases must be found. While the implications of low serum B12 levels aren't always clinical, the case here suggests that vitamin B12 levels aren't being properly monitored.

Vitamin B12 deficiency is both preventable and treatable. In the general population over 50, Evatt et al found a dose-response reduction in B12 deficiency by daily B12 intake. At 6µgs daily or less the prevalence of B12 deficiency was 1.9%; at greater than 25µgs daily it dropped to 0.2% [16]. In diabetics with metformin-associated B12 deficiency, previous cases were successfully treated with B12 injections at 1000 µgs [25, 29, 31, 33]. In our stratified analysis of B12 intake by deficiency, we observed a dose-dependent effect where at intake levels of 100 µgs per day or higher there were no cases (Table 5). For diabetics on metformin with a daily B12 dose of 6 µgs of less, the most common amount in vitamin supplements, there seemed to be no effect. For diabetics not on metformin and for the non-

diabetic population, taking the same amount reduced the prevalence of low B12 levels by at least 50% compared to not taking any B12 at all. The data here suggest a need for more information on this topic. How much of a daily B12 supplement is required to overcome the effects of metformin? This is a reasonable research area to study prospectively in a metformin-taking population with low serum B12 levels. In addition, further information is needed on the clinical aspects of vitamin B12 deficiency. What other outcomes are linked to it and is it at all related to quality of life? This information would be important for both clinicians and patients.

Among diabetics, there were no cases of low serum B12 at B12 supplement levels of 100µgs or higher. However, among the non-diabetics, there were 7 cases of low serum B12 at levels of daily B12 intake of 100µgs or higher. The reason behind this difference cannot be certain, although this may represent a difference in medical access and treatment. Diabetics must frequent the doctor's office more often during the year, and therefore are more likely to be recognized and treated for low B12 levels. On the other side, non-diabetics may not seek medical care and we may be missing cases of B12 deficiency and, as suggested by these cases taking large amounts of B12, pernicious anemia.

In our investigation of individual risk factors predicting vitamin B12 deficiency, metformin was a significant predictor among diabetics after controlling for age, race, sex, and antacid use (Table 6). At odds ratios of over 2, metformin puts diabetics at a two-fold higher risk of both B12 deficiency and borderline deficiency. The logistic regression models also demonstrated the protective effect of B12 supplements against B12 depletion. Taking supplements reduced the risk of B12 deficiency and borderline deficiency by 70% in older non-diabetic adults and by 50% in diabetics not taking metformin. The effect of supplements on diabetics taking metformin was protective, but not significantly. This is most likely attributable to the small sample size. There were only 40 cases of B12 deficiency, and of those cases, only 13 (33%) were taking B12 supplements.

An unexpected result of our analysis arose in the comparison of non-diabetics to diabetics not taking metformin (Table 4). In this diabetic population, the overall health seems exceptionally well. These diabetics are not solely insulin-dependent; most are taking oral medications such as sulfonylurea. The prevalence of B12 deficiency and borderline deficiency was much lower than expected. Perhaps in this group, being diabetic is a protective factor against B12 deficiency. It is reasonable to hypothesize that this group of individuals has regular medical attention and is thus being monitored and treated for low serum B12. However, the real cause of this apparent health effect is unknown.

The strengths of this study include its population-based, nationally representative sample, its detailed information on supplement usage and amount, and its relevant biochemical markers. This is the first study of its kind to examine the relationship between the amounts of daily B12 intake and the prevalence of low serum B12 in diabetics taking metformin. The results suggest that levels of 100µgs or higher are the most effective, where levels between 6 and 100µgs are around 50% effective. As a public health recommendation, diabetic patients on metformin should have their serum B12 levels monitored, and the appropriate treatment plan should be discussed with their health care providers.

There are several limitations to this study. First, NHANES is a cross-sectional survey, and despite its strengths in representativeness, it cannot assess time as a factor and therefore the results are associations and not causal relationships. A second limitation arises in our definition of B12 deficiency. A more accurate definition would include elevated MMA levels. Due to missing data (MMA was not recorded for years 2005-2006), we had to exclude MMA in our outcome definition. Third, we cannot explain the biological characteristics of the diabetic population not taking metformin. We can only speculate as to their unusually low rates of B12 deficiency.

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TABLES

Table 1. Summary of Previous Studies Documenting the Metformin-B12 Relationship

Randomized Control Trials			
Design	**Time**	**Change in B12**	**Reference**
Metformin vs. Placebo	29 weeks	-22% (p N/A)	DeFronzo 1995[19]
Metformin vs. Glyburide vs. Both		-29% (p N/A)	
Metformin vs. Placebo	4.3 years	-19% (p<.001)	de Jager 2010[24]
Metformin vs. Rosiglitazone vs. Lifestyle	6 weeks	-9% (p=.119)	Sahin 2005[39]
Metformin vs. Placebo, +insulin therapy	16 weeks	-14% (p<.0001)	Wulffelé 2003[38]
Metformin vs. Sulfonylurea	12 weeks	-29% (p<.0005)	Bauman 2000[20]
Metformin vs. Placebo in males with CVD	12 weeks	-13.4% (p<.001)	Carlsen 1997[40]
Cross-Sectional Surveys			
Design	**Time on Metformin**	**Change in B12**	**Reference**
Patients on Metformin at least one year	Avg 5.2 years	-27% (p<.01)	Hermann 2004[28]
Type 2 Diabetics - Metformin users vs. non-users	N/A	-19% (p=.01)	Pflipsen 2009[36]
Patients on Metformin at least two years	N/A	-26% (p>.05)	Tomkin 1971[29]
Patients on Metformin at least six months	Median 2.7 years	-27% (p=.011)	Pongchaidecha 2004[41]
Patients on Metformin with Peripheral Neuropathy	N/A	-52.5% (p<.001)	Wile 2010[30]

Table 2. Demographic and Biological Characteristics of Type 2 Diabetics: NHANES 1999-2006

	US Adults Over 50 – Type 2 Diabetics		
	Taking Metformin	**Not Taking Metformin**	**p-value**
N	575	1046	
Age	63.4 (.46)**	66.4 (.46)	**<.0001**
Gender (M)	293 (50.3%)	507 (43.7%)	0.0848
Race: NH White	226 (66.7%)	415 (65.9%)	0.182
NH Black	135 (14.6%)	272 (15.4%)	
Hispanic	188 (10.9%)	323 (13.3%)	
Other	26 (7.8%)	36 (5.5%)	
Current Smoker	76 (26.60%)	115 (23.46%)	0.552
Drinks Alcohol	56 (17.13%)	83 (20.40%)	0.4736
BMI: <25	87 (15.0%)	178 (18.3%)	0.0987
25-<30	196 (29.5%)	361 (33.6%)	
>30	269 (55.5%)	441 (48.1%)	
Duration Diabetes (years)	11.97 (.81)	14.11 (.56)	**0.0207**
Insulin Use	90 (15.4%)	318 (32.3%)	**<.0001**
Supplement Use	285 (56.2%)	536 (59.2%)	0.3458
Folic Acid Supplements	201 (39.6%)	336 (38.1%)	0.6359
B12 Supplements	209 (40.7%)	360 (40.1%)	0.864
Serum Folate (nmol/L)	36.77 (1.42)	42.18 (1.67)	0.121
Homocysteine	9.83 (.17)	10.36 (.28)	0.1051
A1C%	7.34 (.11)	7.26 (.08)	0.5222
Hemoglobin (g/dL)	13.92 (.08)	14.09 (.09)	0.121
Serum B12 (pmol/L)*	317.49 (9.58)	386.73 (7.81)	**0.0116**
B12 Deficiency (<148pmol/L)	25 (5.46%)	15 (2.05%)	**0.0325**
B12 Borderline (148-221pmol/L)	76 (12.79%)	73 (6.10%)	**0.0066**
Low B12 (<221pmol/L)	101 (17.94%)	88 (7.94%)	**0.0004**
Macrocytosis	12 (1.9%)	35 (2.7%)	0.4577
Antacid Use	45 (9.9%)	52 (6.6%)	0.0784
Anemia	104 (16.2%)	222 (17.1%)	0.6594
PPIs	60 (11.7%)	113 (12.3%)	0.7819
H2 Blockers	24 (4.0%)	64 (6.2%)	0.1356

*Geometric Mean; **Cells include survey N and weighted proportions for categorical variables or standard error for continuous variables

Table 3. Demographic and Biological Characteristics of Type 2 Diabetics on Metformin vs. Non-diabetics: NHANES 1999-2006

	US Adults Over 50		
	Type 2 Diabetics on Metformin	**Non-Diabetics**	p-value
N	575	6851	
Age	63.4 (.46)	63.4 (.21)	0.9446
Gender (M)	293 (50.25%)	3382 (45.48%)	0.0961
Race			**<.0001**
NH White	226 (66.73%)	4177 (81.32%)	
NH Black	135 (14.56%)	1110 (7.88%)	
Hispanic	188 (10.90%)	1387 (7.14%)	
Other	26 (7.81%)	193 (3.66%)	
Current Smoker	76 (26.60%)	997 (28.66%)	0.8046
Drinks Alcohol	56 (17.13%)	838 (20.49%)	0.2264
BMI	32 (.36)	28.1 (.10)	**<.0001**
<25	87 (15.02%)	2059 (31.52%)	
25-<30	196 (29.46%)	2546 (37.82%)	
>30	269 (55.52%)	1994 (30.66%)	
Use Supplement	285 (56.21%)	4129 (65.42%)	**0.0031**
Folic Acid Supplements	201 (39.57%)	2873 (47.32%)	**0.0069**
B12 Supplements	209 (40.67%)	2912 (47.48)	**0.018**
Serum Folate (nmol/L)	36.77 (1.42)	38.58 (.56)	0.2398
Homocysteine	9.83 (.17)	9.68 (.08)	0.3702
A1C%	7.34 (.11)	5.5 (.01)	**<.0001**
Hemoglobin (g/dL)	13.92 (.08)	14.44 (.04)	**<.0001**
Serum B12 (pmol/L)*	317.49 (9.58)	350.79 (2.93)	**0.0011**
B12 Deficiency (<148pmol/L)	25 (5.46%)	212 (3.28%)	0.1603
B12 Borderline (148-221pmol/L)	76 (12.79%)	761 (11.42%)	0.5039
Low B12 (<221pmol/L)	101 (17.94%)	973 (14.54%)	0.1697
Macrocytosis	12 (1.85%)	346 (4.54%)	**0.0017**
Antacid Use	45 (9.94%)	553 (9.55%)	0.7986
Anemia	104 (16.16%)	731 (8.04%)	**<.0001**
PPIs	60 (11.66%)	690 (10.53%)	0.5315
H2 Blockers	24 (3.99%)	221 (3.23%)	0.5278

*Geometric Mean

Table 4. Demographic and Biological Characteristics of Type 2 Diabetics not on Metformin vs. Non-diabetics: NHANES 1999-2006

	Type 2 Diabetics Not on Metformin	**Non-Diabetics**	p-value
N	1046	6851	
Age	66.4 (.46)	63.4 (.21)	**<.0001**
Gender (M)	507 (43.7%)	3382 (45.48%)	0.4135
Race			**<.0001**
NH White	415 (65.9%)	4177 (81.32%)	
NH Black	272 (15.4%)	1110 (7.88%)	
Hispanic	323 (13.3%)	1387 (7.14%)	
Other	36 (5.5%)	193 (3.66%)	
Current Smoker	115 (23.46%)	997 (28.66%)	0.081
Drinks Alcohol	83 (20.40%)	838 (20.49%)	0.9815
BMI	31.2 (.39)	28.1 (.10)	**<.0001**
<25	178 (18.3%)	2059 (31.52%)	
25-<30	361 (33.6%)	2546 (37.82%)	
>30	441 (48.1%)	1994 (30.66%)	
Use Supplement	536 (59.2%)	4129 (65.42%)	**0.0078**
Folic Acid Supplement	336 (38.1%)	2873 (47.32%)	**<.0001**
B12 Supplement	360 (40.1%)	2912 (47.48)	**0.0022**
Serum Folate (nmol/L)	42.18 (1.67)	38.58 (.56)	**0.0413**
Homocysteine	10.36 (.28)	9.68 (.08)	**0.0175**
A1C%	7.26 (.08)	5.5 (.01)	**<.0001**
Hemoglobin (g/dL)	14.09 (.09)	14.44 (.04)	**<.0001**
Serum B12 (pmol/L)*	386.73 (7.81)	350.79 (2.93)	0.083
B12 Deficiency (<148pmol/L)	15 (2.05%)	212 (3.28%)	**0.0257**
B12 Borderline (148-221pmol/L)	73 (6.10%)	761 (11.42%)	**<.0001**
Low B12 (<221pmol/L)	88 (7.94%)	973 (14.54%)	**<.0001**
Macrocytosis	35 (2.7%)	346 (4.54%)	**0.0468**
AntacidUse	52 (6.6%)	553 (9.55%)	0.0905
Anemia	222 (17.1%)	731 (8.04%)	**<.0001**
PPIs	113 (12.3%)	690 (10.53%)	0.2512
H2 Blockers	64 (6.2%)	221 (3.23%)	**0.0108**

*Geometric Mean

Table 5. Average Daily B12 Intake by Serum B12 Levels

US Adults Over 50 **Type 2 Diabetics Taking Metformin**				
Serum B12 (pmol/L)	Total	Deficient N(%) <148pmol/L	Depleted N(%) 148-221pmol/L	Total Low N(%) <221 pmol/L
B12 MCG/Day				
No B12	344	16 (4.65%)	62 (18.02%)	78 (22.67%)
>0 - 6 µgs	63	6 (9.52%)	9 (14.29%)	15 (23.81%)
>6 - 25 µgs	71	2 (2.82%)	3 (4.23%)	5 (7.04%)
>25 - 100 µgs	28	1 (3.57%)	2 (7.14%)	3 (10.71%)
>100 - 500 µgs	9	0 (0%)	0 (0%)	0 (0%)
>500 - 1000 µgs	7	0 (0%)	0 (0%)	0 (0%)
>1000 µgs	5	0 (0%)	0 (0%)	0 (0%)

US Adults Over 50 **Type 2 Diabetics Not Taking Metformin**				
Serum B12 (pmol/L)	Total	Deficient N(%) <148pmol/L	Depleted N(%) 148-221pmol/L	Total Low N(%) <221pmol/L
B12 MCG/Day				
No B12	600	10 (1.67%)	59 (9.83%)	69 (11.50%)
>0 - 6 µgs	97	0 (0%)	6 (6.19%)	6 (6.19%)
>6 - 25 µgs	132	4 (3.03%)	5 (3.79%)	9 (6.82%)
>25 - 100 µgs	39	0 (0%)	1 (2.56%)	1 (2.56%)
>100 - 500 µgs	18	0 (0%)	0 (0%)	0 (0%)
>500 - 1000 µgs	18	0 (0%)	0 (0%)	0 (0%)
>1000 µgs	3	0 (0%)	0 (0%)	0 (0%)

US Adults Over 50 **Non-Diabetics**				
Serum B12 (pmol/L)	Total	Deficient N(%) <148pmol/L	Depleted N(%) 148-221pmol/L	Total Low N(%) <221pmol/L
B12 MCG/Day				
No B12	3675	164 (4.81%)	601 (17.56%)	765 (22.37%)
>0 - 6 µgs	1003	19 (1.79%)	73 (7.45%)	92 (9.24%)
>6 - 25 µgs	1021	22 (2.35%)	54 (4.10%)	76 (6.45%)
>25 - 100 µgs	364	3 (.54%)	13 (3.57%)	16 (4.11%)
>100 - 500 µgs	171	2 (.11%)	3 (2.67%)	5 (2.78%)
>500 - 1000 µgs	71	0 (0%)	2 (1.34%)	2 (1.34%)
>1000 µgs	36	0 (0%)	0 (0%)	0 (0%)

Table 6. Multiple Logistic Regressions for Potential Risk Factors of Vitamin B12 Deficiency					
		Type 2 Diabetics		Non-Diabetics	
		B12 <148pmol/L OR (95% CI)	**B12 <221pmol/L** OR (95% CI)	**B12 <148pmol/L** OR (95% CI)	**B12 <221pmol/L** OR (95% CI)
Metformin Use	Yes	**2.66 (1.22-5.77)**	**2.22 (1.25-3.96)**		
	No	1.00 (Ref)	1.00 (Ref)		
Age		1.02 (.99-1.06)	1.01 (.98-1.04)	**1.01 (1.00-1.03)**	1.00 (.99-1.01)
Gender	Male	1.37 (.65-2.86)	1.39 (.84-2.32)	.87 (.64-1.18)	.94 (.77-1.15)
	Female	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Race/Ethnicity	NH White	2.62 (.88-7.82)	1.09 (.61-1.93)	**3.09 (1.60-5.98)**	**1.36 (1.08-1.71)**
	NH Black	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Hispanic	1.07 (.27-4.33)	.63 (.24-1.65)	**2.81 (1.21-6.52)**	1.28 (.88-1.86)
	Other	1.17 (.12-11.47)	.18 (.02-1.40)	**4.53 (1.53-13.41)**	.81 (.41-1.58)
Duration of Diabetes		.98 (.95-1.01)	1.00 (.98-1.02)		
PPI Use	Yes	1.03 (.31-3.43)	1.04 (.52-2.07)	.67 (.35-1.28)	.94 (.70-1.27)
	No	1.00(Ref)	1.00 (Ref)	1.00(Ref)	1.00 (Ref)
H2 Blocker Use	Yes	1.99 (.57-6.92)	.77 (.26-2.25)	.74 (.25-2.17)	1.37 (.80-2.34)
	No	1.00(Ref)	1.00 (Ref)	1.00(Ref)	1.00 (Ref)
Insulin Use	Yes	.46 (.16-1.31)	.61 (.33-1.11)		
	No	1.00(Ref)	1.00 (Ref)		
B12 Supplement	Yes	.93 (.41-2.11)	**.47 (.25-.88)**	**.32 (.21-.48)**	**.30 (.24-.38)**
	No	1.00(Ref)	1.00 (Ref)	1.00(Ref)	1.00 (Ref)
Antacid Use	Yes	2.47 (.62-9.81)	**2.45 (1.13-5.33)**	.48 (.17-1.34)	**.60 (.44-.81)**
	No	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Metformin Use, Model 1		**2.73 (1.20-6.18)**	**2.20 (1.22-3.99)**		

Model 1: Adjusted for Age, Race, Gender, and Antacid Use

Table 7: Type 2 Diabetics: Vitamin B12 Deficient Cases (N=40)

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
296	72	Female	Other	24.7	31	31.06	0.374	0.6	11.1	33.2	Yes	Yes
297	75	Female	Black	97.4	34.69	156.3	35.96	1.5	10.4	28.4	Yes	Yes
298	73	Female	White	60.2	49.45	123.19	7.59	0.7	13.6	40.3	No	No
299	70	Male	Hispanic	24.9	55.35	55.61	10.558	0.6	14.8	42.9	No	No
300	75	Female	White	20.2	61.25	25.03	2.183	1	13.9	41.2	No	No
301	60	Female	Hispanic	21.1	69.37	14.5	0.76	0.6	12.2	36.5	No	No
302	82	Male	White	32.2	69.37	15.87	.	1	14.7	44.2	No	No
303	81	Female	White	48	70.11	9.53	.	1	12.1	36.6	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
296	6.5	19.83	Yes	0	No	0	No	No	.	0	No	No
297	12.9	20.24	Yes	.	Yes	.	Yes	No	.	.	Yes	No
298	5.1	33.98	Yes	12	Yes	400	Yes	Yes	Yes	10	Yes	No
299	9.3	25.73	No	0	No	0	No	No	.	0	No	No
300	5.1	22.22	Yes	12.5	Yes	50	Yes	Yes	Yes	751	Yes	No
301	7.1	33.83	Yes	0	No	0	No	No	.	0	No	No
302	5.9	29.63	No	0	No	0	No	No	.	0	No	No
303	6.8	20.19	No	0	No	0	No	No	.	0	No	No

	Take insulin	Take H2 blocker?	Take PPI?	Take diabetes RX?	Take Metformin	Time Taking Met?	Take Other Oral?	Age Diabetes DX	Years with Diabetes
296	No	No	No	Yes	Yes	5-10yr	No	66	6
297	Yes	No	No	Yes	No	.	No	55	20
298	No	No	No	.	No	.	.	73	0
299	Yes	No	No	Yes	No	.	Yes	56	14
300	No	No	No	.	No	.	.	73	2
301	Yes	No	No	Yes	Yes	10+yr	No	50	10
302	No	No	No	Yes	Yes	10+yr	No	73	9
303	No	No	No	Yes	Yes	5-10yr	No	72	9

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
304	71	Male	White	75.9	74.54	14.33	.	1	15	45.3	No	No
305	75	Male	Hispanic	24.7	74.54	23	.	1.2	15.9	47.4	No	No
306	77	Male	Hispanic	22.9	89.3	13	.	0.8	14.3	40.9	No	No
307	79	Female	White	27.6	97.42	10.95	0.129	0.7	12.1	36.8	No	No
308	70	Female	Hispanic	28.1	101.11	20.45	.	1	13.5	39.9	No	No
309	56	Male	White	29.9	103.32	15.3	.	1.2	14.4	41.4	No	No
310	50	Male	White	19.7	105.53	23.92	.	0.9	14.6	42.2	No	No
311	62	Male	White	27	109.96	14.39	0.218	1.3	13.6	39.6	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
304	5.9	25.58	Yes	25	Yes	400	Yes	No	.	200	Yes	No
305	6.9	30.32	No	0	No	0	No	No	.	0	No	No
306	6	22.62	Yes	25	Yes	400	Yes	No	.	200	Yes	No
307	6.8	24.61	No	0	No	0	No	No	.	0	No	No
308	6.3	27.93	Yes	25	Yes	400	Yes	No	.	200	Yes	No
309	5.7	29.51	Yes	6	Yes	400	Yes	No	.	162	Yes	No
310	5.1	41.05	No	0	No	0	No	No	Yes	0	No	No
311	6.9	44.54	Yes	0	No	0	No	No	.	185	Yes	No

	Take insulin ?	Take H2 blocker?	Take PPI?	Take diabetes RX?	Take Metformin?	Time Taking Met?	Take Other Oral?	Age Diabetes DX	Years with Diabetes
304	No	No	No	Yes	No	.	Yes	65	6
305	No	No	No	Yes	No	.	Yes	60	15
306	No	No	No	Yes	Yes	1-3yr	No	67	10
307	No	No	No	Yes	Yes	10+yr	No	69	10
308	No	No	No	Yes	Yes	10+yr	No	51	19
309	No	No	No	Yes	Yes	5-10yr	No	42	14
310	No	Yes	Yes	Yes	Yes	6-12mo	No	40	10
311	No	No	No	Yes	Yes	5-10yr	No	58	4

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
312	62	Male	White	20.2	109.96	19.8	0.596	1.2	15	44.1	No	No
313	62	Male	White	19.3	110.7	12.73	0.366	0.8	16.6	48.1	No	No
314	59	Male	Hispanic	39.9	114.39	8.32	0.113	0.7	15.4	46.2	No	No
315	67	Male	Black	20.6	121.03	6.07	0.138	0.8	14.5	45.7	No	No
316	65	Female	White	83.4	121.77	15.37	0.25	0.6	14.5	42.6	No	No
317	65	Female	White	49.6	122.51	11.48	0.22	0.9	14.7	43.4	No	No
318	78	Male	White	18.8	126.94	28.82	0.715	1.2	12.1	36.8	No	Yes
319	70	Female	Black	40.3	126.94	10.38	.	0.7	13.3	39.5	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
312	5.7	34.91	Yes	6	Yes	400	Yes	No	.	162	Yes	No
313	5.9	29.76	No	0	No	0	No	Yes	Yes	0	No	No
314	7.1	28.09	No	0	No	0	No	No	.	0	No	No
315	13.7	21.44	No	0	No	0	No	No	.	0	No	No
316	8.5	24.26	Yes	6	Yes	400	Yes	No	.	1362	Yes	No
317	6.6	41.1	Yes	0	No	0	No	No	.	1800	Yes	No
318	5.7	30.83	No	0	No	0	No	No	.	0	No	No
319	7	31.44	No	0	No	0	No	No	.	0	No	No

	Take insulin ?	Take H2 blocker?	Take PPI?	Take diabetes RX?	Take Metformin?	Time Taking Met?	Take Other Oral?	Age Diabetes DX	Years with Diabetes
312	No	No	No	Yes	Yes	5-10yr	No	56	6
313	No	No	No	Yes	Yes	0-3mo	No	57	5
314	No	No	No	Yes	Yes	10+yr	No	53	6
315	Yes	No	No	Yes	No	.	No	57	10
316	No	Yes	No	Yes	Yes	10+yr	No	45	20
317	Yes	No	No	Yes	Yes	1-3yr	No	38	27
318	No	Yes	No	Yes	Yes	1-3yr	No	74	4
319	No	No	Yes	Yes	Yes	1-3yr	No	68	2

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
320	70	Female	Hispanic	29.9	128.41	15.9	.	0.9	13.8	40.5	No	No
321	60	Male	Black	36.2	129.89	14.82	0.12	1.2	12.7	37.3	No	Yes
322	60	Male	Black	36.2	129.89	14.82	0.12	1.2	12.7	37.3	No	Yes
323	71	Male	White	21.5	130.63	15.86	0.235	1.2	16.2	48.3	No	No
324	62	Female	Black	.	130.63	15.33	.	0.8	11.4	36.1	No	Yes
325	80	Female	White	28.5	130.63	15.6	.	0.8	12	36.4	No	No
326	68	Male	White	26.7	132.1	21.5	.	1.4	13.2	39.8	No	No
327	58	Male	White	12	134.32	9.59	.	0.9	15.7	46.2	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
320	6.5	43.76	No	0	No	0	No	No	.	0	No	No
321	7	38.11	No	0	No	0	No	No	.	0	No	No
322	7	38.11	No	0	No	0	No	No	.	0	No	No
323	6.6	26.76	No	0	No	0	No	Yes	Yes	0	No	No
324	10.3	32.88	No	0	No	0	No	No	.	0	No	No
325	6.5	23.49	Yes	0.2	Yes	13.333	Yes	No	.	25.4	Yes	No
326	6.4	26.76	Yes	0	No	0	No	Yes	Yes	48	Yes	No
327	6	31.75	Yes	0	No	0	No	No	.	0	No	No

	Take insulin ?	Take H2 blocker?	Take PPI?	Take diabetes RX?	Take Metformin?	Time Taking Met?	Take Other Oral?	Age Diabetes DX	Years with Diabetes
320	No	No	No	Yes	No	.	Yes	45	25
321	No	No	No	Yes	No	.	Yes	57	3
322	No	No	No	Yes	Yes	1-3yr	No	57	3
323	No	No	No	Yes	No	.	Yes	69	2
324	No	No	No	Yes	Yes	10+yr	No	50	12
325	No	No	No	Yes	Yes	10+yr	No	60	20
326	No	No	Yes	Yes	No	.	Yes	60	8
327	No	No	No	Yes	No	.	Yes	58	0

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
328	82	Male	White	13.1	137.27	12.36	0.438	1	13.9	39.9	No	No
329	58	Male	White	16.3	138.01	13.99	0.265	1	14.5	42.2	No	No
330	51	Female	White	27.9	140.96	9.21	0.23	1	14.1	41.2	No	No
331	70	Male	White	20.6	142.43	14.56	0.44	1.1	16.5	47.8	No	No
332	72	Male	White	22.2	142.43	20.44	0.158	1.2	14.1	41.7	Yes	No
333	65	Male	White	38.1	143.17	10.96	0.126	1	13.5	39.7	No	No
334	70	Female	Hispanic	29.4	143.17	11.9	.	0.5	14.7	45.5	No	No
335	67	Female	White	66.8	144.65	10.68	0.614	0.9	12.8	37.4	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
328	6.2	.	No	0	No	0	No	No	.	0	No	No
329	6.2	35.94	No	0	No	0	No	No	.	0	No	No
330	8.5	33.29	Yes	27	Yes	800	Yes	Yes	Yes	576	Yes	No
331	7.8	44.48	No	0	No	0	No	No	.	0	No	No
332	6.1	31.99	Yes	0.9333	Yes	62.221	Yes	No	.	513.33	Yes	No
333	7.1	38.67	Yes	6	Yes	400	Yes	No	.	0	No	No
334	6.7	31.41	No	0	No	0	No	No	.	0	No	No
335	6.4	39.6	Yes	12.5	Yes	450	Yes	No	.	1984	Yes	Yes

	Take insulin ?	Take H2 blocker?	Take PPI?	Take diabetes RX?	Take Metformin?	Time Taking Met?	Take Other Oral?	Age Diabetes DX	Years with Diabetes
328	No	No	Yes	Yes	Yes	10+yr	No	77	5
329	Yes	No	Yes	Yes	Yes	10+yr	No	10	48
330	No	No	No	Yes	Yes	6-12mo	No	47	4
331	Yes	No	No	Yes	No	.	No	38	32
332	No	No	No	Yes	Yes	3-5yr	No	62	10
333	No	No	No	Yes	Yes	10+yr	No	55	10
334	No	No	No	Yes	No	.	Yes	67	3
335	No	No	No	Yes	No	.	Yes	61	6

Table 8: Type 2 Diabetics: Borderline B12 Deficient Cases (N=149)

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
336	65	Male	Hispanic	30.8	148.34	8.77	0.222	0.8	15.4	45.6	No	No
337	70	Male	White	20.8	149.08	27.47	0.04	0.6	14.2	41.7	No	No
338	70	Male	White	20.8	149.08	27.47	0.04	0.6	14.2	41.7	No	No
339	71	Female	White	22.4	149.81	21.74	0.307	1.4	11.2	33.7	No	Yes
340	81	Male	White	45.3	150.55	9.3	0.19	0.5	12.9	37.6	No	Yes
341	62	Female	Black	12.9	150.55	8.96	.	0.8	11.4	36.3	No	Yes
342	82	Female	White	66.4	151.29	31.21	0.948	1.4	12.1	35.8	No	No
343	66	Female	Hispanic	22.7	152.03	18.12	0.44	1.2	12.7	37.6	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
336	7	27.55	Yes	0	No	0	No	Yes	Yes	225	Yes	No
337	9	29.02	Yes	100	Yes	400	Yes	No	.	0	No	No
338	9	29.02	Yes	100	Yes	400	Yes	No	.	0	No	No
339	6.6	37.94	No	0	No	0	No	No	.	0	No	No
340	8.4	28	No	0	No	0	No	No	.	0	No	No
341	6.9	31.72	No	0	No	0	No	No	.	0	No	No
342	7.8	19.84	Yes	6	Yes	400	Yes	No	.	662	Yes	No
343	5.5	34.29	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
336	Yes	No	No	Yes	10+yr	No	55	10
337	No	No	No	Yes	6-12mo	No	69	1
338	No	No	Yes	No		Yes	69	1
339	Yes	No	No	No		No	60	11
340	No	No	No	Yes	3-5yr	No	50	31
341	No	No	No	Yes	1-3yr	No	60	2
342	Yes	No	No	No		No	54	28
343	No	No	No	Yes	0-3mo	No	.	.

#	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
344	66	Female	Hispanic	22.7	152.03	18.12	0.44	1.2	12.7	37.6	No	No
345	80	Female	Hispanic	55.3	152.03	17.74	0.32	1	15	46.4	No	No
346	60	Male	White	30.6	153.5	7.8	.	1.1	14.9	44.1	No	No
347	74	Male	White	31.5	154.24	13.09	0.21	1	12.7	38	No	Yes
348	74	Male	White	31.5	154.24	13.09	0.21	1	12.7	38	No	Yes
349	70	Male	Black	24.5	154.24	14.5	.	1.2	12.9	36.9	No	Yes
350	58	Male	Other	24.7	154.98	11.1	.	0.7	15.1	47.4	No	No
351	72	Female	White	24.5	154.98	8.87	.	0.8	14.1	41.7	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
344	5.5	34.29	No	0	No	0	No	No	.	0	No	No
345	6.6	18.99	No	0	No	0	No	No	.	0	No	No
346	7	42.46	Yes	25	Yes	400	Yes	No	.	200	Yes	No
347	9.5	23.09	No	0	No	0	No	No	.	0	No	No
348	9.5	23.09	No	0	No	0	No	No	.	0	No	No
349	6.3	30.29	No	0	No	0	No	No	.	0	No	No
350	11.7	.	No	0	No	0	No	No	.	0	No	No
351	7.4	29.17	Yes	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
344	No	No	No	No		Yes	.	.
345	No	No	No	Yes	10+yr	No	65	15
346	Yes	No	Yes	Yes	10+yr	No	43	17
347	No	Yes	No	No		Yes	72	2
348	No	No	No	No		Yes	72	2
349	No	No	Yes	Yes	1-3yr	No	69	1
350	No	Yes	Yes	Yes	5-10yr	No	51	7
351	No	No	Yes	Yes	10+yr	No	55	17

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
352	53	Male	White	73.8	156.46	8.26	0.27	0.8	15.7	46.3	No	No
353	78	Female	White	56.6	156.46	10.85	.	0.8	14.6	43.6	No	No
354	65	Female	Hispanic	58.2	157.19	10.68	0.207	0.8	11.7	34.7	No	Yes
355	81	Female	White	14	157.93	13.4	0.31	1	12.7	37.6	No	No
356	53	Female	Hispanic	17.4	157.93	7.54	0.193	0.6	11.9	34	No	Yes
357	69	Male	Black	22.2	160.15	14.23	0.16	1	11.3	33.6	No	Yes
358	72	Male	White	11.6	162.36	9.43	0.3	0.9	16.5	48.3	No	No
359	85	Male	Hispanic	27.9	164.57	16.99	0.329	1.3	15.4	44.8	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
352	6	37.15	Yes	30	Yes	400	Yes	Yes	Yes	200	Yes	No
353	6.4	26.79	Yes	6	Yes	400	Yes	Yes	Yes	228.67	Yes	No
354	7.1	32.59	Yes	25	Yes	400	Yes	No	.	200	Yes	No
355	6	.	No	0	No	0	No	No	.	0	No	No
356	7.6	27.39	Yes	0	No	0	No	No	.	600	Yes	No
357	7	23.78	No	0	No	0	No	No	.	0	No	No
358	9.6	27.3	Yes	5.921	Yes	394.74	Yes	No	.	0	No	No
359	8	28.8	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
352	No	No	No	Yes	10+yr	No	42	11
353	No	No	No	Yes	10+yr	No	64	14
354	Yes	No	No	No		No	38	27
355	No	No	No	Yes	10+yr	No	70	11
356	Yes	No	Yes	No		No	39	14
357	No	No	Yes	Yes	10+yr	No	60	9
358	.	Yes	No	No		Yes	60	12
359	Yes	No	No	No		No	85	0

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
360	73	Male	White	16.8	164.57	16.3	.	1.4	13.4	40.9	No	No
361	72	Male	Hispanic	15.2	166.05	12.12	0.22	0.8	13.8	41.7	No	No
362	76	Female	White	19.7	166.05	11.3	0.374	1.2	12.4	37.3	No	No
363	76	Male	Black	15.9	166.05	12.35	.	1.4	12.9	38.2	No	Yes
364	52	Male	White	57.3	166.79	19.2	0.898	1	14.2	42.7	No	No
365	78	Female	White	82.4	167.53	10.56	.	0.9	13.5	38.8	No	No
366	62	Male	White	15.9	168.26	13.07	0.139	1	14.9	42.8	No	No
367	51	Female	White	39.6	169	6.06	.	0.8	13.5	38.3	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
360	6	35.16	Yes	0	No	0	No	No	.	0	No	No
361	7	.	No	0	No	0	No	No	.	0	No	No
362	5.8	30.75	No	0	No	0	No	No	.	0	No	No
363	8.1	30.51	No	0	No	0	No	Yes	Yes	0	No	No
364	5.2	37.66	Yes	12	Yes	800	Yes	Yes	Yes	2000	Yes	No
365	7.8	22.86	Yes	0	No	0	No	No	.	500	Yes	No
366	5.5	26.21	No	0	No	0	No	No	Yes	0	No	No
367	6.3	38.07	Yes	6	Yes	400	Yes	No	.	450	Yes	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
360	No	No	No	No		Yes	10	63
361	Yes	No	No	Yes	6-12mo	No	6	66
362	Yes	No	Yes	No		No	45	31
363	Yes	No	No	Yes	10+yr	No	48	28
364	No	No	No	No		.	40	12
365	No	No	No	Yes	5-10yr	No	73	5
366	No	No	No	No		Yes	59	3
367	No	No	Yes	Yes	10+yr	No	49	2

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
368	71	Male	White	16.5	170.48	14.99	1.62	.	11.5	34.7	No	Yes
369	79	Female	White	22.7	170.48	11.39	0.146	0.8	13	38.7	No	No
370	69	Female	Black	24.5	170.48	10.3	.	0.9	13.4	41.3	No	No
371	77	Female	Black	17.7	171.22	13.59	0.225	1	11.8	35.7	No	Yes
372	69	Female	Black	25.8	171.95	11.28	.	1.2	9.8	30.7	No	Yes
373	66	Male	Black	26.7	172.69	22.9	.	1.6	13.6	40.2	No	No
374	64	Male	Hispanic	28.3	173.43	9.17	0.15	0.9	14.8	42.2	No	No
375	65	Female	White	18.6	174.17	13.72	0.359	0.9	15.3	45.1	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
368	7.9	.	Yes	0	No	0	No	No	.	.	Yes	No
369	5.6	28.12	Yes	0	No	0	No	No	.	0	No	No
370	8.4	27.63	No	0	No	0	No	No	Yes	0	No	Yes
371	7.2	35.91	Missing	.	.	.	.	No	.	.	.	No
372	7.3	55.12	Yes	0	No	0	No	No	.	0	No	Yes
373	8.5	31.13	No	0	No	0	No	No	.	0	No	No
374	5.8	26.19	No	0	No	0	No	No	.	0	No	No
375	8.6	30.8	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
368	Yes	No	Yes	No		Yes	60	11
369	No	Yes	No	No		Yes	74	5
370	No	No	No	Yes	6-12mo	No	62	7
371	No	No	No	No		.	.	.
372	Yes	No	Yes	No		No	40	29
373	No	No	No	Yes	10+yr	No	50	16
374	No	No	No	No		Yes	56	8
375	Yes	No	No	No		.	30	35

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
376	57	Female	White	13.6	174.17	15.91	0.209	0.9	12.2	36.3	No	No
377	60	Male	Other	32.6	174.91	15.04	0.43	1	14.3	41.6	No	No
378	61	Male	Hispanic	39.2	174.91	10.98	0.56	0.7	15.4	46.1	No	No
379	68	Male	Hispanic	41.2	174.91	6.96	0.138	0.9	17.5	51	No	No
380	70	Female	Hispanic	22	174.91	10.5	0.286	0.6	11.9	37.1	No	Yes
381	66	Male	Hispanic	29.4	175.64	11.51	0.27	0.8	16.3	48.3	No	No
382	74	Female	Hispanic	26.5	175.64	14.84	0.38	0.9	14.3	42.9	No	No
383	68	Male	White	22.4	175.64	12.63	0.591	0.9	15.2	44.5	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
376	6	25.97	No	0	No	0	No	No	.	0	No	No
377	8.6	22.82	No	0	No	0	No	No	.	0	No	No
378	8.9	37.49	Yes	.	Yes	.	Yes	No	.	.	Yes	No
379	8.7	25.59	No	0	No	0	No	Yes	Yes	0	No	No
380	7.6	29.96	No	0	No	0	No	No	.	0	No	No
381	9.3	25.74	No	0	No	0	No	No	.	0	No	No
382	7.2	40.16	Yes	0	No	0	No	No	.	.	Yes	No
383	6.5	53.6	Yes	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
376	No	No	No	Yes	3-5yr	No	52	5
377	No	No	No	Yes	10+yr	No	27	33
378	No	No	No	No		Yes	59	2
379	No	No	No	No		Yes	62	6
380	No	No	No	Yes	5-10yr	No	40	30
381	No	No	No	Yes	6-12mo	No	50	16
382	Yes	No	No	No		No	30	44
383	No	No	Yes	Yes	3-5yr	No	60	8

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
384	50	Male	White	32.4	176.38	20.65	1.077	1.1	15.8	48.3	No	No
385	80	Male	White	58.9	177.12	10.73	0.188	1	12.7	38.1	Yes	Yes
386	70	Male	Black	25.4	177.12	12.9	.	1	13	39.4	No	No
387	60	Female	White	27	178.6	7.68	0.16	0.7	13.2	37.8	No	No
388	54	Male	Black	15.2	179.33	8.18	0.15	1.1	13.5	40.2	No	No
389	79	Female	Black	16.5	180.81	9.41	0.13	0.5	11.4	34.2	No	Yes
390	82	Male	White	49.2	181.55	12.69	0.339	1.1	15.3	45.2	No	No
391	69	Male	White	19.3	183.76	13.6	0.179	1.2	16.7	48.4	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
384	8.1	24.74	No	0	No	0	No	Yes	Yes	0	No	No
385	6	35.42	Yes	0	No	.	Yes	No	.	0	No	No
386	6.7	25.34	No	0	No	0	No	No	.	0	No	No
387	7.2	45.37	No	0	No	0	No	No	.	0	No	No
388	9.3	28.86	No	0	No	0	No	No	.	0	No	No
389	4.5	17.43	No	0	No	0	No	No	.	0	No	No
390	6.9	23.42	Yes	6	Yes	400	Yes	No	.	162	Yes	No
391	6	38.48	Yes	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
384	Yes	No	No	No		.	20	30
385	No	Yes	No	No		Yes	18	62
386	No	No	No	Yes	5-10yr	No	62	8
387	No	No	No	Yes	6-12mo	No	59	1
388	Yes	No	No	No		No	48	6
389	No	No	No	No		.	79	0
390	No	No	No	Yes	10+yr	No	73	9
391	No	No	No	No		.	68	1

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
392	83	Female	White	66.6	183.76	11.1	.	0.8	12.6	38.7	No	No
393	61	Male	Hispanic	22.7	183.76	13.4	.	1.3	14.4	42.5	No	No
394	79	Male	Black	25.6	184.5	10.05	0.1	1	11.9	37	No	Yes
395	79	Male	Black	25.6	184.5	10.05	0.1	1	11.9	37	No	Yes
396	85	Female	White	21.1	184.5	16.77	0.85	1.1	14.5	44.4	No	No
397	56	Male	White	31	184.5	8.49	.	0.8	14.1	41.5	No	No
398	62	Female	Hispanic	20.8	185.24	14.72	0.44	1.1	13.5	39.1	No	No
399	62	Female	Hispanic	20.8	185.24	14.72	0.44	1.1	13.5	39.1	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
392	6.3	23.11	Yes	25	Yes	400	Yes	Yes	Yes	906.67	Yes	No
393	8.1	33.01	No	0	No	0	No	No	.	0	No	No
394	5.6	36.2	Yes	0	No	0	No	No	.	0	No	No
395	5.6	36.2	Yes	0	No	0	No	No	.	0	No	No
396	6.2	23.05	No	0	No	0	No	No	.	0	No	No
397	8.4	36.26	No	0	No	0	No	Yes	Yes	0	No	No
398	6.8	25.91	No	0	No	0	No	No	.	0	No	No
399	6.8	25.91	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
392	No	No	No	Yes	10+yr	No	70	13
393	Yes	Yes	No	Yes	10+yr	No	59	2
394	No	No	No	No		Yes	62	17
395	No	No	No	Yes	5-10yr	No	62	17
396	No	No	No	No		Yes	50	35
397	No	No	No	Yes	3-5yr	No	50	6
398	No	No	Yes	No		Yes	58	4
399	No	No	No	Yes	1-3yr	No	58	4

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
400	60	Female	Hispanic	24.9	185.98	11.73	0.219	0.7	14.1	43.2	No	No
401	60	Female	Hispanic	29.2	185.98	11.9	.	0.9	12.1	37.3	No	No
402	63	Female	White	29	185.98	11.1	.	1.1	12.3	37.1	No	No
403	64	Female	Hispanic	62.5	186.71	9.88	.	0.8	11	34.3	No	Yes
404	62	Male	Hispanic	24.7	188.19	7.74	0.14	0.7	14.1	41.8	No	No
405	62	Male	Hispanic	24.7	188.19	7.74	0.14	0.7	14.1	41.8	No	No
406	62	Male	Hispanic	24.7	188.19	7.74	0.14	0.7	14.1	41.8	No	No
407	65	Male	Hispanic	31.3	188.19	11.87	0.13	1.1	14.5	43.5	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
400	7.5	29.36	No	0	No	0	No	No	.	0	No	No
401	8.2	38.81	Yes	0	No	0	No	No	.	.	Yes	No
402	6.4	37.55	Yes	0	No	0	No	No	.	0	No	No
403	8	24.41	Yes	0.6	Yes	40	Yes	No	.	16.2	Yes	No
404	7.7	28.28	No	0	No	0	No	No	.	0	No	No
405	7.7	28.28	No	0	No	0	No	No	.	0	No	No
406	7.7	28.28	No	0	No	0	No	No	.	0	No	No
407	6.6	29.51	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
400	No	No	No	No		Yes	.	.
401	Yes	No	Yes	Yes	6-12mo	No	44	16
402	No	No	No	Yes	10+yr	No	49	14
403	No	No	No	Yes	5-10yr	No	59	5
404	No	No	No	No		Yes	50	12
405	No	No	No	Yes	1-3yr	No	50	12
406	No	No	No	No		Yes	50	12
407	No	No	No	Yes	5-10yr	No	50	15

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
408	64	Female	Black	10.2	188.19	16.32	0.25	0.7	13.1	39.2	No	No
409	62	Female	Black	31.5	188.19	.	.	1.2	11.6	34.5	No	Yes
410	64	Male	White	26.5	188.93	9.7	0.15	1.3	15.1	45.5	No	No
411	78	Female	Black	20.6	188.93	15.58	0.479	1.3	11.3	32.8	No	Yes
412	59	Male	White	13.8	190.4	11.01	.	1.1	14.1	42	No	No
413	61	Male	Hispanic	19.7	191.14	13.24	0.374	0.9	12.5	36.5	No	Yes
414	74	Male	Hispanic	20.2	191.88	11.94	0.15	0.8	16	47.9	No	No
415	67	Female	White	74.7	191.88	9.82	0.176	0.8	12.7	37.4	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
408	5.9	25.67	No	0	No	0	No	No	.	0	No	No
409	7.3	32.2	Yes	25	Yes	400	Yes	Yes	Yes	320	Yes	No
410	8.3	35.39	Yes	0	No	0	No	No	.	0	No	No
411	6.6	32.73	No	0	No	0	No	No	.	0	No	No
412	8	31.52	No	0	No	0	No	No	.	0	No	No
413	6.5	37.78	No	0	No	0	No	No	.	0	No	No
414	7.7	36.63	No	0	No	0	No	No	.	0	No	No
415	6.2	35.04	Yes	6	Yes	1220	Yes	No	.	222	Yes	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
408	No	No	No	No		.	61	3
409	No	No	No	Yes	10+yr	No	55	7
410	Yes	No	No	No		No	54	10
411	No	No	No	Yes	10+yr	No	72	6
412	Yes	No	No	Yes	10+yr	No	47	12
413	Yes	No	No	Yes	5-10yr	No	54	7
414	No	No	No	No		Yes	68	6
415	No	No	No	Yes	5-10yr	No	63	4

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
416	51	Male	White	27	191.88	7.91	0.171	.	15.1	44.1	No	No
417	84	Male	White	29.2	191.88	14.1	.	1.4	15	45.7	Yes	No
418	75	Male	Black	14.9	192.62	16.25	0.23	1.2	11.8	37.4	No	Yes
419	58	Female	Black	18.6	192.62	7.96	.	1	13.8	41.1	No	No
420	62	Female	Black	17.9	193.36	7.73	0.098	0.6	13.1	40.2	No	No
421	76	Male	White	28.8	193.36	12.94	0.306	1.1	15.3	44.9	No	No
422	76	Male	White	48.9	194.09	10.51	0.198	1	16.5	49.3	No	No
423	78	Male	Black	17.7	194.09	33.93	.	1.7	12.5	36.8	Yes	Yes

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
416	5.7	28.83	No	0	No	0	No	No	.	0	No	No
417	6.4	27.01	No	0	No	0	No	No	.	0	No	No
418	6.5	37.13	No	0	No	0	No	No	.	0	No	No
419	6.4	47.52	No	0	No	0	No	Yes	Yes	0	No	No
420	8.4	27.99	No	0	No	0	No	No	.	0	No	No
421	7.4	34.41	Yes	0	No	0	No	No	.	0	No	No
422	5.6	37.21	Yes	6	Yes	400	Yes	No	.	162	Yes	No
423	4.7	29.18	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
416	No	No	No	No		.	50	1
417	Yes	No	No	No		No	74	10
418	Yes	No	No	No		No	60	15
419	No	No	No	Yes	1-3yr	No	56	2
420	No	No	No	Yes	5-10yr	No	48	14
421	Yes	No	No	Yes	5-10yr	No	46	30
422	No	No	No	No		.	62	14
423	Yes	No	No	No		.	.	.

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
424	60	Male	Hispanic	12	194.83	13.6	.	1.1	15	43.4	No	No
425	68	Male	White	38.5	195.57	7.65	0.162	0.7	14.4	43.4	No	No
426	84	Female	Black	30.4	195.57	10.1	.	1	12.8	38.1	No	No
427	69	Female	Hispanic	74.7	196.31	11.12	0.14	0.5	14.5	44.4	No	No
428	69	Female	Hispanic	74.7	196.31	11.12	0.14	0.5	14.5	44.4	No	No
429	52	Male	Hispanic	14.5	196.31	9.21	.	0.8	14.3	42.5	No	No
430	79	Female	Hispanic	21.1	197.05	15.54	0.468	0.7	13.4	40.5	No	No
431	63	Male	Black	21.3	197.05	10.9	.	1.2	12.7	36.8	No	Yes

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
424	9	37.38	Yes	0	No	0	No	No	.	540	Yes	No
425	6.2	33.19	Yes	6	Yes	1410	Yes	No	.	192	Yes	No
426	5.3	35.54	No	0	No	0	No	No	.	0	No	No
427	10.3	26.61	Yes	3	Yes	200	Yes	No	.	7.5	Yes	No
428	10.3	26.61	Yes	3	Yes	200	Yes	No	.	7.5	Yes	No
429	4.4	25.74	No	0	No	0	No	No	.	0	No	No
430	7	35.94	No	0	No	0	No	No	.	0	No	No
431	5.4	29.82	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
424	Yes	No	No	Yes	10+yr	No	48	12
425	No	No	No	Yes	5-10yr	No	58	10
426	No	No	No	No		Yes	60	24
427	No	No	No	No		Yes	58	11
428	No	No	No	Yes	1-3yr	No	58	11
429	No	No	No	No		.	42	10
430	No	No	No	No		Yes	59	20
431	No	No	No	No		.	63	0

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
432	55	Female	Black	14.7	197.05	9.42	.	0.8	12.8	38.5	No	No
433	85	Male	White	29.7	197.78	14.5	0.24	1.4	16.2	48.7	No	No
434	85	Female	White	15.2	197.78	10.74	0.31	0.7	12	35.8	No	No
435	58	Female	Black	14.9	198.52	11.39	0.17	0.7	11.8	34.8	No	Yes
436	67	Female	Hispanic	24.7	200	10.58	0.45	0.4	14.7	43.5	No	No
437	81	Male	White	14.9	200	15.76	0.39	1.2	16	46.2	No	No
438	82	Male	White	16.3	200	12.2	.	1	13.3	39.2	No	No
439	81	Female	Black	42.6	200.74	11.81	0.23	0.8	12.8	39.9	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
432	6.5	23.73	No	0	No	0	No	No	.	0	No	No
433	5.7	24.99	Yes	10	Yes	100	Yes	Yes	Yes	.	Yes	No
434	7.5	29.82	Yes	0	No	0	No	No	.	0	No	No
435	6.3	39.21	Yes	0	No	0	No	No	.	0	No	No
436	5.9	28.78	No	0	No	0	No	No	Yes	0	No	No
437	6.6	29.04	No	0	No	0	No	No	.	0	No	No
438	7.2	21.18	No	0	No	0	No	No	.	0	No	No
439	6.5	27.61	No	0	No	0	No	Yes	Yes	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
432	No	No	No	Yes	6-12mo	No	55	0
433	No	No	No	No		.	68	17
434	No	No	Yes	Yes	6-12mo	No	81	4
435	No	No	No	Yes	3-5yr	No	37	21
436	Yes	No	Yes	No		Yes	66	1
437	No	No	No	Yes	0-3mo	No	40	41
438	No	No	No	Yes	6-12mo	No	70	12
439	No	No	Yes	No		Yes	60	21

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
440	81	Female	Black	42.6	200.74	11.81	0.23	0.8	12.8	39.9	No	No
441	60	Female	White	16.1	200.74	6.6	.	0.6	14.5	43.4	No	No
442	82	Female	White	92.2	201.47	9.25	0.42	0.5	14.6	43.4	No	No
443	85	Male	White	16.8	201.47	9.71	.	0.8	14.8	44.1	No	No
444	61	Female	Hispanic	36.7	202.21	5.31	0.04	0.5	15	44.4	No	No
445	64	Female	Black	14	202.21	13.88	0.139	1	12.2	35.8	No	No
446	71	Female	Hispanic	24.7	203.69	10.71	0.14	1	14.8	44.3	No	No
447	63	Male	White	44.4	204.43	7.31	0.14	1.2	16.8	48.8	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
440	6.5	27.61	No	0	No	0	No	Yes	Yes	0	No	No
441	6.5	49.01	No	0	No	0	No	No	.	0	No	No
442	7.4	35.82	No	0	No	0	No	No	.	0	No	No
443	6.5	30.94	No	0	No	0	No	No	.	0	No	No
444	10.9	33.69	No	0	No	0	No	No	.	0	No	No
445	8.1	34.08	No	0	No	0	No	No	.	0	No	No
446	6	36.49	No	0	No	0	No	No	.	0	No	No
447	5.8	30.72	Yes	25	Yes	400	Yes	No	.	200	Yes	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
440	No	No	No	Yes	1-3yr	No	60	21
441	No	No	No	Yes	1-3yr	No	55	5
442	No	No	No	No		.	63	19
443	No	No	No	Yes	5-10yr	No	66	19
444	No	No	No	No		Yes	54	7
445	No	No	No	No		Yes	7	57
446	No	Yes	No	No		Yes	71	0
447	No	No	No	No		Yes	.	.

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
448	68	Male	Hispanic	20.2	204.43	8.82	0.108	0.9	15	45.3	No	No
449	64	Male	White	18.3	204.43	8.9	.	1.1	15.4	46.1	No	No
450	78	Male	White	31.5	204.43	10.12	.	1.1	14.1	41.2	No	No
451	62	Male	Hispanic	30.1	205.9	14.99	0.256	1.2	15.1	44.7	No	No
452	81	Female	White	19	205.9	13.43	.	1	14.6	44.3	No	No
453	64	Male	Hispanic	33.3	205.9	7.42	.	0.8	16.7	49.2	No	No
454	82	Female	White	207.9	206.64	7.82	0.13	0.8	15.8	46.6	No	No
455	82	Female	White	207.9	206.64	7.82	0.13	0.8	15.8	46.6	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
448	8	25.15	No	0	No	0	No	No	.	0	No	No
449	8.2	37.82	Yes	0	No	0	No	Yes	Yes	44	Yes	No
450	6	33.03	No	0	No	0	No	No	.	0	No	No
451	10.3	42.53	No	0	No	0	No	No	.	0	No	No
452	6.9	23.59	No	0	No	0	No	Yes	Yes	0	No	No
453	5.9	32.72	No	0	No	0	No	No	.	0	No	No
454	8	27.61	Yes	6	Yes	400	Yes	No	.	5.4	Yes	No
455	8	27.61	Yes	6	Yes	400	Yes	No	.	5.4	Yes	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
448	No	No	No	Yes	5-10yr	No	48	20
449	No	No	No	Yes	10+yr	No	45	19
450	No	No	No	No		.	70	8
451	No	No	No	No		.	58	4
452	No	No	No	Yes	1-3yr	No	78	3
453	No	No	No	Yes	6-12mo	No	41	23
454	No	Yes	No	No		Yes	78	4
455	No	No	No	No		Yes	78	4

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
456	50	Male	Hispanic	25.6	206.64	7.91	.	0.9	16.4	46.2	No	No
457	68	Female	White	22.7	208.85	8.73	0.15	0.5	13.8	39.1	No	No
458	56	Male	White	28.1	209.59	7.32	0.12	0.5	15	44.2	No	No
459	80	Male	Hispanic	19.5	210.33	11.88	0.2	1.3	12.3	35.3	No	Yes
460	70	Female	White	21.7	210.33	6.05	0.08	0.5	12.9	41.4	No	No
461	61	Male	Black	18.3	210.33	10.92	.	1.1	14.8	45	No	No
462	76	Female	White	43.5	211.07	14.69	0.21	1	14.2	42.5	No	No
463	85	Female	Black	20.2	212.54	18.04	0.25	1.2	10.9	33.3	No	Yes

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
456	7.4	27.98	Yes	7.5	Yes	400	Yes	No	.	300	Yes	No
457	7.3	28.74	No	0	No	0	No	No	.	0	No	No
458	6.6	53.1	Yes	0	No	0	No	No	.	0	No	No
459	6	23.31	No	0	No	0	No	No	.	0	No	No
460	8.1	32.01	Yes	0	No	0	No	No	.	0	No	No
461	6.3	31.53	No	0	No	0	No	No	.	0	No	No
462	6.5	38.47	Yes	0	No	0	No	No	.	500	Yes	No
463	9.5	.	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
456	No	No	No	No		.	48	2
457	No	No	No	Yes	0-3mo	No	55	13
458	No	No	No	Yes	1-3yr	No	35	21
459	No	No	No	No		.	14	66
460	No	No	No	No		Yes	65	5
461	No	No	No	No		.	59	2
462	No	No	No	Yes	0-3mo	No	64	12
463	Yes	No	No	No		No	67	18

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
464	85	Female	Black	20.2	212.54	18.04	0.25	1.2	10.9	33.3	No	Yes
465	85	Female	Black	20.2	212.54	18.04	0.25	1.2	10.9	33.3	No	Yes
466	74	Male	White	25.6	212.54	9.81	0.25	0.8	14.6	42.2	No	No
467	76	Female	Hispanic	30.1	213.28	15.08	0.21	0.8	11.1	33.9	No	Yes
468	76	Female	Hispanic	30.1	213.28	15.08	0.21	0.8	11.1	33.9	No	Yes
469	71	Male	Black	27.4	213.28	12.66	0.15	1.1	13.4	39	No	No
470	57	Female	Black	35.8	213.28	8.08	0.15	0.8	14	39.8	No	No
471	73	Male	White	22.7	214.76	7.04	0.161	0.8	15	45.3	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
464	9.5	.	No	0	No	0	No	No	.	0	No	No
465	9.5	.	No	0	No	0	No	No	.	0	No	No
466	6.4	32.7	No	0	No	0	No	No	.	0	No	No
467	10.2	29.95	No	0	No	0	No	No	.	0	No	Yes
468	10.2	29.95	No	0	No	0	No	No	.	0	No	Yes
469	9	.	No	0	No	0	No	No	.	0	No	No
470	13.9	24.88	No	0	No	0	No	No	.	0	No	No
471	8.1	42.87	Yes	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
464	Yes	No	No	Yes	5-10yr	No	67	18
465	Yes	No	No	No		Yes	67	18
466	No	No	Yes	Yes	1-3yr	No	73	1
467	No	No	No	Yes	6-12mo	No	25	51
468	No	No	No	No		Yes	25	51
469	Yes	No	No	No		No	50	21
470	No	No	No	Yes	5-10yr	No	50	7
471	No	No	No	No		Yes	67	6

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
472	62	Male	Black	20.2	215.5	13.31	0.17	1.3	15.1	44.9	No	No
473	63	Male	White	27.9	215.5	8.17	0.114	0.9	15.6	45.7	No	No
474	85	Female	White	34.7	215.5	10.29	.	1	13.9	39.2	No	No
475	69	Male	Black	19	215.5	10.4	.	0.9	15.5	48.2	No	No
476	57	Female	White	53	215.5	8.96	.	0.8	13.5	39.4	No	No
477	73	Male	White	74.7	216.23	16.02	0.39	0.8	16.6	49.2	No	No
478	51	Female	Black	25.6	216.23	6.26	0.12	0.5	12.5	37.7	No	No
479	61	Male	White	26.3	216.23	10.6	.	0.9	14.9	42.7	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
472	7	32.85	No	0	No	0	No	No	.	0	No	No
473	5.9	29.71	No	0	No	0	No	No	.	0	No	No
474	6.5	30.52	No	0	No	0	No	No	.	0	No	No
475	10.8	29.04	No	0	No	0	No	No	Yes	0	No	No
476	6.7	35.77	Yes	6	Yes	400	Yes	No	.	162	Yes	No
477	5.8	25.49	Yes	0	No	0	No	No	.	0	No	No
478	7.1	30.74	No	0	No	0	No	No	.	0	No	No
479	7.1	27.74	No	0	No	0	No	No	.	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
472	Yes	No	No	No		No	48	14
473	No	No	No	Yes	6-12mo	No	57	6
474	No	No	No	No		Yes	.	.
475	No	No	No	Yes	5-10yr	No	57	12
476	No	No	No	Yes	10+yr	No	45	12
477	No	No	No	No		.	10	63
478	No	No	No	No		Yes	48	3
479	No	No	No	Yes	6-12mo	No	60	1

	Age	Gender	Race	Serum Folate nmol/L	Serum B12 pmol/L	Hcys umol/L	MMA umol/L	Creatinine mg/dL	Hemoglobin g/dL	Hematocrit %	Macrocytosis	Anemia
480	65	Female	Hispanic	42.8	216.97	7.39	0.06	0.4	14.4	42.6	No	No
481	54	Male	White	24.5	216.97	9.16	0.145	0.9	15.1	45.2	No	No
482	85	Male	White	20.2	216.97	14.37	0.234	1.2	12.9	38.4	No	Yes
483	61	Female	White	19.5	218.45	9.66	0.151	0.6	13.2	38.6	No	No
484	61	Female	Hispanic	14.7	220.66	7.7	.	0.6	14.3	42.4	No	No

	A1C%	BMI	Take Supp?	Avg ugs B12/Day	Take B12?	Avg ugs Folate/Day	Take Folic Acid?	Take antacid 3+yr?	Take antacid now?	Avg ugs Calcium/Day	Take Calcium?	Take RX for anemia?
480	8.3	30.22	Yes	0	No	0	No	No	.	125	Yes	No
481	9.5	36.43	No	0	No	0	No	No	.	0	No	No
482	8.1	21.24	Yes	0	No	0	No	No	.	0	No	No
483	5.6	34.57	Yes	6	Yes	400	Yes	Yes	Yes	295.33	Yes	No
484	9.9	35.54	No	0	No	0	No	Yes	Yes	0	No	No

	Take insulin?	Take H2 blocker?	Take PPI?	Take metformin?	Time Taking Met?	Take other oral DIA rx?	Age Diabetes DX	Years with Diabetes
480	No	No	No	Yes	6-12mo	No	63	2
481	No	No	Yes	Yes	5-10yr	No	50	4
482	No	No	No	No		Yes	15	70
483	No	No	No	Yes	6-12mo	No	60	1
484	Yes	Yes	No	Yes	10+yr	No	35	26

SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

There are three important findings from this analysis. First, vitamin B12 supplements reduce B12 deficiency by approximately 50%. Second, there is a clear relationship between metformin and reduced levels of serum B12 among type 2 diabetics over the age of 50. Third, there are potentially untreated and undiagnosed cases of pernicious anemia in the adult US population that need to be found.

This analysis suggests a need for further research in two areas: vitamin B12 supplements and metformin, and the clinical outcomes of low serum B12. For the first area, the relationship between the amount of daily B12 and its subsequent ability to overcome the affects of metformin needs to be elucidated. This is a reasonable area for a prospective study among metformin users with low B12 levels. Second, the clinical applications of reduced serum B12 need greater exploration. Rare events such as megaloblastic anemia and B12-related peripheral neuropathy provide clear indications of the need to treat deficient B12, but further research is needed into the effects of borderline deficiency.