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Li Wei Date

Exploring Risk Factors for Vitamin D Deficiency in Cystic Fibrosis Patients and Generally healthy Population

By

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Exploring Risk Factors for Vitamin D Deficiency in Cystic Fibrosis Patients and Generally healthy Population

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Li Wei

Ph. D.
Chinese Academy of Sciences, Wuhan China
2007

Thesis Committee Chair: Limin Peng, Ph.D.
Theis Committtee Member: Yuan Liu, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2014

Abstract

Exploring Risk Factors for Vitamin D Deficiency in Cystic Fibrosis Patients and Generally healthy Population

By Li Wei

This study is aimed to explore and compare the risk factors of vitamin D deficiency in cystic fibrosis patients and generally healthy population. Our data included 95 cystic fibrosis patients recruited from Emory hospital and Emory clinic, and 719 healthy subjects recruited from Predictive Health Initiative cohort established within the Center for Health Discovery and Well Being. Vitamin D deficiency was defined by the concentration of serum 25[OH]D less than 30 ng/mL. We performed univariate analyses to examine the marginal effect of each potential risks factor on vitamin D deficiency. Multivariate logistic regression models were built subsequently to depict the association between vitamin D deficiency and its significant risk factors. For healthy subjects, the results showed that race other than black, being older, more sun exposure, supplement vitamin D intake, taking physical activity, and lower total body mass are associated with lower risk of vitamin D deficiency. For CF patients, we only identify race and season as important risk factors for vitamin D deficiency and their effects are consistent to those in healthy people. The comparison between the findings based on the CF cohort and those based on the healthy cohort suggests that, the efficient ways to reduce the risk of vitamin D deficiency in healthy subjects, such as increasing sun exposure, taking supplement D with low or middle dose, and lowering the body fat, may not be successful in correcting the low concentration of vitamin D in cystic fibrosis patients. The effective treatment to vitamin D deficiency in CF patients needs to be investigated with further relevant studies.

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1. Background

Cystic Fibrosis

Cystic fibrosis (CF) is the most common life threatening and hereditary disease among caucasians in United States (Krauth, Jalilvand et al. 2003). This disorder affects the lungs and digestive system of about 70,000 children and adults in the world. It is caused by mutations in a gene on chromosome 7 encoding the CFTR protein, which functions as a chloride channel within a number of epithelial tissues (Riordan, Rommens et al. 1989, Collins 1992). Delta F508 is the most common CFTR gene mutation with which CF patients could be subcategorized into heterozygous and homozygous carriers (Johansen, Nir et al. 1991).

Morbidity and mortality in cystic fibrosis patients is mainly due to progressive lung disease and recurrent pulmonary infections (Grossmann, Zughaier et al. 2012). The mutative and malfunctioned CFTR gene and its protein product cause the body to produce abnormally thick and sticky mucus that clogs the lungs and consequently leads to life-threatening lung infections; and obstructs the pancreas and stops natural enzymes from helping the body break down and absorb food known as pancreatic insufficiency.

Vitamin D

Vitamin D is a group of fat soluble secosteroids responsible for enhancing intestinal absorption of minerals and chemicals such as calcium, iron, magnesium, phosphate and zinc (Lieben and Carmeliet 2013). For human, cholecalciferol (D3) and ergocalciferol (D2) are two most important compounds in this group which can be ingested from the

diet and from supplements (Tripkovic, Lambert et al. 2012). The body can also synthesize vitamin D from cholesterol in the skin with an adequate sun exposure (Poskitt, Cole et al. 1979).

It is well recognized that adequate stores of vitamin D are crucial for musculoskeletal health (Holick 2004, Weng, Shults et al. 2007). There have been many literatures about the effect of vitamin D on health. For older people, taking vitamin D with higher doses may decrease fracture risk (Bischoff-Ferrari, Willett et al. 2012). For young children, vitamin D deficiency causes osteomalacia and have been related with falls and low bone mineral density (Cranney, Horsley et al. 2007). In general, vitamin D has the capability to activate the innate and dampen the adaptive immune system. Vitamin D deficiency has been linked to increased risk of viral infections, including HIV and influenza (Hewison 2011, Spector 2011). A diet with insufficient vitamin D in combination with inadequate sun exposure causes impaired bone mineralization and bone damage leading to the bone softening diseases (Grant and Holick 2005).

Vitamin D Deficiency

The best indicator of vitamin D stores is the serum concentration of calcidiol or 25-hydroxyvitamin D [25(OH)D] (Hollis 1996, Heaney 1999). When the concentration of circulating [25(OH)D] is low, a state known as hypovitaminosis D, intestinal calcium absorption and bone mineralization are impaired. More severe insufficiency of [25(OH)D] could lead to clinical myopathy, osteomalacia in adults and rickets in children (Sahay and Sahay 2012).

Hypovitaminosis D remains an under recognized problem in the general population and in children. Several recent studies have reported that inadequate circulating 25(OH)D concentration in adult medical inpatients (Thomas, Lloyd-Jones et al. 1998), postmenopausal women (Holick, Siris et al. 2005), and free living adults (Tangpricha, Pearce et al. 2002). In the pediatric population, several studies have reported low serum vitamin D concentrations in adolescents living in Boston, Cleveland, and Maine (Gordon, DePeter et al. 2004, Harkness and Cromer 2005), in infants and toddlers in Alaska(Gessner, Plotnik et al. 2003), and in children of primary school age in Lebanon (El-Hajj Fuleihan, Nabulsi et al. 2001). Obesity in children and general population were also shown to be significantly associated with the decreased concentration of circulating 25(OH)D (Botella-Carretero, Alvarez-Blasco et al. 2007, Walker, Ricotti et al. 2014). In addition, prior studies did not examine the relations between vitamin D deficiency and multi risk factors as a whole including race, body composition, and calcium supplements intake, social economic status, individual disease history, daily physical activity in healthy adult population.

Adults and children with cystic fibrosis have a high prevalence of Multi-Vitamin deficiency despite increased awareness and guidelines for treatment of vitamins deficiency (Boyle, Noschese et al. 2005, Wolfenden, Judd et al. 2008, Khazai, Judd et al. 2009). Vitamin D deficiency may be particularly quite common in the CF population. The patients with cystic fibrosis could have the greater risk of several unhealthy conditions having strong associations with vitamin D deficiency including: low bone mineral density, diabetes, decreased lung function, respiratory infections and dysregulation of the adaptive and innate immune response (Jeffery, Burke et al. 2009,

Kamen and Tangpricha 2010, Urashima, Segawa et al. 2010, Pincikova, Nilsson et al. 2011). Therefore, monitoring the concentration of vitamin D in the CF patients and identifying risk factors for the vitamin D deficiency in CF patients will help doctors diagnose vitamin D lowering and provide quick response for treatment in an effective and efficiency way resulting in benefitting the CF patients by improving their clinical outcomes.

Vitamin D deficiency could happen in healthy people. Several published papers have reported that location of healthy subjects and the level of exposure to sun could affect the concentration of serum vitamin D concentration (Gessner, Plotnik et al. 2003, Robberecht, Vandewalle et al. 2011). There is question whether the cystic fibrosis patients will have different risk factors or the disease of cystic fibrosis could modify the risk factors. In order to address this question, we also recruited another group of healthy people. The healthy participates are attendants in the Emory/Georgia Tech Predictive Health Initiative cohort established within the Center for Health Discovery and Well Being. The Emory-Georgia Tech Center for Health Discovery and Well Being is part of an innovative model of health care called predictive health. This center takes a unique, multi-dimensional approach to learning more about health and well being, and then provides the expertise to help people define goals. The main purpose is to improve the participants' health instead of to treat some specific diseases. Those who were recruited in our current study from this program, mainly are coming from employee and the family members at Emory University. The comprehensive physical information are collected for those participants including the concentration of vitamin D, demographics, supplements reporting, social history, blood work et al.

Statement of Research Questions

In current research project, our goal is to attain a comprehensive understanding about the association between vitamin D deficiency and the potential risk factors for providing an efficient and effective way to help clinic doctors monitor the probability of having vitamin D deficiency and provide quick response and treatment for people.

First, we identify the risk factors on vitamin D deficiency in patients with cystic fibrosis disease, a sample of CF patients diagnosed and treated at Emory hospital and Emory clinic. Secondly, we are targeting the risk factors significantly associated with the lower concentration of serum vitamin D in generally healthy people. Finally, we will compare those risk factors affecting vitamin D deficiency in those two populations.

2. Data and Methods

Data Source and Study Design

Data on CF Patients

The data were generated from a retrospective research study conducted by Dr. Tangpricha at Emory University. For cystic fibrosis patients selection, medical records (both paper and electronically documents) of all cystic fibrosis patients who had been treated in the Emory Clinic and Emory Hospital from 2008-2012 were reviewed. To identify these subjects, Dr. Tangpricha's group examined the medical records of patients seen at Emory CF center. Qualified subjects were given a unique patient identifier number after selection for study to maintain confidentiality. Our final data on CF patients included 95 subjects with variables on sex, age, CF gene mutation, pancreatic insufficiency, body mass index (BMI), the concentrations of serum of 25(OH)D, season of visit and the dose of vitamin D supplement intake.

Generally Healthy People

Participants in our healthy group were generally healthy adults (ages 18 and older) recruited between January 2008and February 2013 to participate in the Emory/Georgia Tech Predictive Health Initiative cohort established within the Center for Health Discovery and Well Being (http://predictivehealth.emory.edu). Recruitment to join the study was based on a random list of all Emory employees as well as leaders from the Emory and Georgia Tech communities. Spouses, family, and friends of Emory Employees were also welcome to join the study for a membership fee. All subjects

applied online and underwent an initial screening process. Exclusion criteria were: hospitalization for acute or chronic disease within the previous year; history of severe psychosocial disorder within the previous year; addition of new prescription medications to treat a chronic condition within the previous year (with the exception of changes in anti-hypertensive or anti-diabetic agents); history of substance/drug abuse or alcoholism within the previous year; current active malignant neoplasm; history of malignancy other than localized basal cell cancer of skin during the previous 5 years; uncontrolled or poorly controlled autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, infectious, inflammatory, musculoskeletal, neurologic, psychiatric or respiratory disease; any acute illness (such as viral infection) in the previous 12 weeks before baseline visits.

Our final data on healthy population included 719 subjects that had participated in this study. In addition to the variables available in our CF data, our data for the healthy group include weight, calcium supplement intake, anthropometrics, social economic status, history of diseases, physical activity and etc..

Outcome Definition

Vitamin D deficiency is defined by serum concentration of 25-hydroxyvitamin D (25(OH)D) levels less than 30 ng/mL. This threshold was selected because serum parathyroid hormone (PTH) rises in healthy individuals when the 25(OH)D level falls below 30 ng/mL. PTH levels > 50 pg/mL are associated with an increased risk of bone loss. Regarding this relationship, the guideline set 30 ng/mL as the cutoff (West, Lechtzin et al. 2011).

A Combined Dataset

We also consider a combined dataset formed by merging our data on CF patients and data on healthy subjects. Only the variables collected in both CF and Healthy group were kept in the combined dataset. A binary variable was created to indicate the status of cystic fibrosis. Therefore, the combined dataset includes variables for vitamin D deficiency, CF status, age, BMI, sex, season, race, and supplement vitamin D intake.

Screening Explanatory Variables and Primary Analysis

All statistical analysis were performed on SAS 9.3. The pipeline of analysis for CF, control groups are same. Firstly, we conducted descriptive analysis for outcome variable (Vitamin D deficiency) and each explanatory variable. After examining the frequencies distribution of each categorical variable and the mean ± standard deviation of numeric variable, univariate association related with vitamin D deficiency and univariate logistic regression model were applied to filter potential important variables. For categorical variables, the contingency table of vitamin D deficiency and each explanatory variable were examined; chi-square test and/or Fisher's exact test were performed to detect if there is a significant association between vitamin D deficiency and each categorical explanatory variable. If any element of contingency table is less than 5, Fisher's exact test will be more preferred than chi-square test. For numeric explanatory variables, two-sample T test were performed to detect if there is a significant difference of numeric explanatory variable between control and CF groups. The significant level was set as 0.05.

In order to explore the modification of the status of cystic fibrosis on the association between other variables and Vitamin D deficiency, we did input all variables and the interaction of CF and each other variable in the initiation of the multivariate logistic regression model and used backward strategy to perform the variable selection.

The significant variables detected by any of univariate association tests or univariate logistic model as the potential risk factors were applied to a multivariate logistic model. Backward selection strategy was performed on variable selection. Selection entry and stay level were 0.1 and the significant level was consistently set as 0.05. Hosmer and lemeshow Goodness of Fit test was conducted to test how well the final logistic model fit the data. The variables fitting in final multivariable logistic regression were selected as the reliable risk factors.

3. Results of Statistical Analysis for CF Group

Descriptive Analysis

The descriptive analysis for cystic fibrosis patients is summarized in Table 1. There was no missing data in our CF dataset. Among the ninety-five adults CF patients (43% Female; age ranging from 19 to 63 years), 46% of them were diagnosed as vitamin D deficiency (25[OH]D< 30 ng/mL). 42% of all CF patients are heterozygous carriers. The range of body mass index (BMI) is from 14.7 to 30.10. All CF patients take the supplement of vitamin D only except one patient. 95.8% CF patients are carrying pancreatic insufficiency. Only 5 out of 95 are black people or African American.

Table 2 shows the univariate association of each explanatory variable with the outcome of Vitamin D deficiency. For categorical explanatory variables, the contingency table along with Chi-square test (parametric p-value) or Fisher's exact test (non-parametric p-value) is produced. If any element of contingency table was less than 5, then the Fisher's exact test result was used instead of the chi-square test. For numerical explanatory variables, two sample T test (parametric p-value) or Kruskal-Wallis test (non-parametric p-value) were carried out. There are no significance for sex, gene mutation, pancreatic insufficiency, supplement intake of vitamin D, age and BMI regarding to the contribution to Vitamin D deficiency. Vitamin D deficiency in CF patients tends to happen in the season of spring or winter rather (less opportunity for sun exposure) than summer or fall (more opportunity for sun exposure). This association is marginally significant (Chi-square P-value=0.079 and Fisher's exact P-value=0.10). Race is a statistically significant risk factor for Vitamin D deficiency in CF patients (Fisher's

exact P-value=0.026). Five Black/AA CF patients are all have the Vitamin D deficiency. This may suggest that black CF patient will have higher risk to have vitamin D deficiency than others.

The results based on the univariate logistic regression in CF patients are summarized in Table 3. The p-value for each explanatory variable is very consistent with univariate association analysis only except Race. The univariate logistic regression for testing the significance of race failed to converge due to the small number of black patients included. Season shows a marginal significance from fitting univariate logistic regression model. CF patients have less risk to obtain the vitamin D deficiency in summer and fall than spring and winter (OR of the exposure to summer and fall to the exposure to spring and winter: 0.482, 95% CI: 0.213~1.094, P-value: 0.081).

According to the above results, two variables "season and race" are included in our final multivariate logistic regression model. The estimates of correlation coefficients are showed in Table 4. As mentioned before, logistic regression analysis may not be reliable for evaluating the effect of race given that our CF data include only a few black subjects. Therefore, the variable race was forced to stay in the final multivariable logistic regression model. The final model is:

$$\text{logit}\,[\,\text{prob}(Y=1)\,] = 0.2877 - 0.6242 * \text{Season} + 13.0625 * \text{Race}$$

where Y=1 means Vitamin D deficiency, 0 means NO Vitamin D deficiency;

Season=1 means "Summer or Fall", 0 means "Spring or Winter";

Race=1 means “Black or African American”, 0 means “Others”.

This model shows that the estimated odds ratio of the exposure to the vitamin D deficiency for Summer and fall versus spring and winter is 0.536 given the same race; the estimated odds ratio of the exposure to the vitamin D deficiency for black race versus non_black race is 470947given the same season.

4. Results of Statistical Analysis for Generally healthy Group

Descriptive Analysis

The descriptive analysis for healthy group was summarized in Table 5. Very few data was missing. Our data include 719 healthy subjects (65% Female; age ranging from 18 to 82 years). 48.8% of healthy subjects were found to have Vitamin D deficiency with the criteria of the concentration of the serum vitamin D less than 30 ng/mL. The dataset for Healthy group contains much richer information than our CF data, including a total of thirty-two explanatory variables such as age, BMI, height, weight, waist, waist to hip ratio, race, season of visit, living condition, social economic status, education level, history of medicines of lowering glucose/lipids/cholesterol/blood-pressure, reported history of relevant diseases (such as diabetes and hypertension), tobacco use, supplements intake (such as vitamin D, calcium, multivitamin), physical activity with different intensive levels. Regarding to the supplements intake, out of 719 subjects 370 took Supplement vitamin D, 226 took multi-vitamin and 160 took supplement Calcium. 95% of all subjects have no tobacco use and/or no reported history of diabetes. 548 (80.5%) of all subjects do not have reported history of hypertension. 558 (81.9%) of all subjects do not have hyperlipidemia. 701 (98.7%) of all subjects are not Hispanic or Latino. We use this group of healthy subjects to represent generally healthy population.

Table 6 shows the univariate association of each explanatory variable with the categorical outcome of Vitamin D deficiency. The statistical tests were similar to those applied in CF group. The results show that twenty-two covariates have the statistically significant association with Vitamin D deficiency. They are sex, race, season, income,

marital status, supplement D intake, supplement calcium, moderate physical activity, vigorous physical activity, tobacco use, reported history of diabetes, reported history of hypertension, blood pressure lowering medicine intake, glucose lowering medicine intake, lipid lowering medicine intake, multi-vitamin intake age, BMI, weight, waist, total composition region fat, total BMD, total body total composition fat. All the p-values for those covariates are less than 0.05. Parametric and non-parametric tests provided very consistent results. Univariate logistic regression was performed to confirm/validate our findings in table 6 and the result was summarized in table 7. Those results are highly consistent with each other.

There are many covariates measured for healthy group. Though the dataset looks very comprehensive, some covariates could have high correlation with each other, such as waist vs. weight, moderate physical activity vs. vigorous physical activity. In order to avoid overfitting the model, backward variable selection strategy was chosen and Variance Inflation Factor (VIF) was calculated under multivariable logistic regression. It is seen as a highly correlation if VIF is bigger than 10.

All the variables with statistical significance (α level is chosen as 0.05) in table 6 and table 7 had no high correlations detected with VIF test and were considered in the multivariable logistic regression modeling. After the backward variable selection, there are six explanatory variables remaining in our final model for the risk of vitamin D deficiency; they are age, total body total composition fat, race, season, supplement D intake, moderate physical activity (Table 8). It seems that an older subject has a lower risk to develop vitamin D deficiency (OR: 0.97, 95%CI: 0.95~0.99, P-value <0.001). Increasing total body total composition fat (measured by DXA) may increase the risk of

Vitamin D lowering (OR: 1.02, 95% CI: 1.02 ~ 1.03, P-value < 0.001). It is less likely to have deficiency of Vitamin D in the seasons of summer and fall than in spring and winter (OR: 0.69, 95% CI: 0.49 ~ 0.98, p-value: 0.041). African American is more likely to have vitamin D deficiency than other race groups (OR: 2.88, 95% CI: 1.83 ~ 4.53, p-value < 0.001). Taking supplement D is statistically significantly and positively decreasing vitamin D deficiency risk (OR: 0.46, 95% CI: 0.32 ~ 0.65, p-value: 0.001). People having the moderate physical activity would be less likely to have Vitamin D deficiency (OR: 0.58, 95% CI: 0.38 ~ 0.88, p-value: 0.010).

Table 9 summarized the estimates of correlation coefficienct for each significant explanatory variable based on the total 625 healthy people observations. The final model is:

logit [prob(Y=1)]=0.4174 - 0.3674 * Season + 1.0568 * Race - 0.7810 * Supplement_D - 0.5444 * Caps_ModeGuide - 0.0308 * Age + 0.0246 * TotFatMass

where

TotFatMass= Total body total composition fat;

Y = 1 means Vitamin D Deficiency, 0 means No Vitamin D Deficiency;

Season=1 means “Summer or Fall”, 0 means “Spring or Winter”;

Race = 1 means “Black or African American”, 0 means “Other”;

Caps_ModeGuide= 1 means Taking Moderate physical activity, 0 means No taking physical activity;

The final model shows the estimated odds ratio of the exposure to the vitamin deficiency for summer and fall versus spring and winter with fixed other variables is 0.6944 indicating the risk of vitamin D deficiency for summer and fall is less than that for spring and winter. The estimated odds ratio of the exposure to the vitamin D deficiency for black race/AA versus others with fixed other variables is 2.877; the estimated odds ratio of the exposure to vitamin D deficiency for healthy people who take supplement vitamin D versus healthy people who don't take with fixed other variable is 0.4579. The estimated odds ratio of the exposure to vitamin D deficiency for healthy people who take moderate physical activity versus the people who don't with fixed other vairables is 0.5802. The odds ratio of the exposure to the vitamin D deficiency with 1 year increase in age with other variables fixed is 0.9697; the odds ratio of the exposure to the vitamin D deficiency with 1-unit increase in total body fat mass with other variables fixed is 1.0245.

5. Results from Combined Dataset

We explored the impact of the disease status of cystic fibrosis on vitamin D deficiency by fitting a multivariate logistic regression model to the combined dataset. In our model building, we always included CF and considered its interaction with each of other explanatory variables. With the backward variable selection, the final model fitted to the combined dataset is presented in Table 10.

logit [prob(Y=1)]= -1.4516 + 3.3965 * CF -0.0216 * Age + 0.1015* BMI - 0.4079 * Season + 1.1349 * Race - 0.7433* Supplement_D – 0.1165 * (CF * BMI)

This model shows the disease of cystic fibrosis (CF factor) and the interaction of CF and BMI (CF * BMI) are significantly associated with vitamin D deficiency (p=0.023 for CF; p=0.072 for CF * BMI). In general, CF patients have higher risk to develop the vitamin D deficiency than the generally healthy people. Given that BMI is equal to 21.7 (mean of BMI in CF patients) and other variables are fixed, the estimated OR of the exposure to CF patients to the exposure to the generally healthy people is 2.3827 (95% CI: 1.3626 ~ 4.1666; p-value: 0.0023).

The interaction of CF and BMI suggests that the association of BMI with vitamin D deficiency in CF patients is different from that in generally healthy people. For generally healthy people, the Odds ratio of the exposure to the vitamin D deficiency with 1-unit increase in BMI is 1.1068 (95% CI: 1.0716 ~ 1.1432; p-value: <0.0001) which means healthy people with higher BMI significantly have higher risk to develop vitamin D

deficiency. However, for CF patients, the odds ratio of the exposure with 1-unit increase in BMI is 0.9851 with no significance (95% CI: 0.8706 ~ 1.1147; p-value: 0.8118) which means increasing BMI in CF patients will not significantly alter the risk to develop the vitamin D deficiency.

6. Discussion

Risk factors for vitamin D deficiency in CF patients

In this study, for our CF patients, 49 out 95 (51.6%) patients had Vitamin D deficiency which means the concentration of serum 25(OH)D level less than 30 ng/mL. All black people or African American (n=5) were diagnosed with Vitamin D deficiency though all of them were taking supplement of vitamin D. Most cases of vitamin D deficiency occurred at winter or spring. The factors of age, sex, BMI, Delta F508 gene mutation and the status of pancreatic insufficiency are not significant for affecting the risk of vitamin D deficiency.

Cystic fibrosis, as the most common autosomal recessive genetic disease in whites, affects multiple organ systems, including the lungs, the exocrine pancreas and the hepatobiliary system. It is reported that approximately 70% ~ 90% of individuals with CF have pancreatic insufficiency. In our CF group, 91 out of 95 (95.8%) patients have PI which is consistent or even higher than the prevalence of PI in CF population. The major consequences of pancreatic insufficiency are due to fat malabsorption, which is caused by decreased production of pancreatic enzymes. As a result, patients are at risk for steatorrhea, malnutrition, and fat-soluble vitamin deficiencies. Treatment of PI includes supplementation with pancreatic enzymes; however, supplementation does not completely correct the fat malabsorption. In addition, in individuals with CF and PI, fat-soluble vitamins (ie, vitamins A, D, E, and K) are malabsorbed (Chavasse, Francis et al. 2004).

Based on our result, taking supplement of vitamin D could not contribute to correct the concentration of serum vitamin D in CF patients which is consistent with recent studies. The main reason may be that most CF patients in this study have pancreatic insufficiency. In 2013, Bertolaso reported that LYM-X-SORB (LXS), an organized lipid matrix, could increase the vitamin A and E but remained vitamin D unchanged for children and young adults with cystic fibrosis and pancreatic insufficiency (Bertolaso, Groleau et al. 2013). Another reason could be due to the inadequate intake of the vitamin D supplement. The median intake of vitamin D is 2000 IU and 90% percentile is 3800 IU. Recent studies about the intake of very high dose of vitamin D have showed that 700,000 IU vitamin intake over 2 weeks significantly increase 25-OH D level in CF children and young adults (Boas, Hageman et al. 2009). A randomized study conducted by Grossmann showed vitamin D intake with a dose 250,000 UI significantly correct vitamin D deficiency in CF adults patients with pancreatic insufficiency; the placebo failed to correct the vitamin D deficiency(Grossmann, Zughaier et al. 2012). However, it has been reported that intake of high dose (400,000 IU) vitamin D could fail in correcting vitamin D deficiency in CF children even though the duration of the treatment was over 2 months(Boyle, Noschese et al. 2005). Though Grossmann's randomized study show no statistically significant difference of PI in treated group and placebo group, the frequency of PI in treated group was lower than in placebo group (86.7% in treated group vs. 100% in placebo group, p-value=0.14). The status of pancreatic insufficiency may modify the effect of supplement vitamin D on correction of vitamin D deficiency.

Cystic fibrosis rarely happens to black people and only 5 black or AA CF patients were found in this current study. However, all these 5 black/AA CF patients have the

vitamin D deficiency. Fisher's exact test showed race is very important risk factor to develop the vitamin D deficiency in CF group. Prior studies have reported that the vitamin D deficiency varies in race for the healthy population and black race people is more voluntary to that (Harkness and Cromer 2005, Weng, Shults et al. 2007).

Our study also showed CF patients in summer and fall are less likely to develop vitamin D deficiency than in sprint and winter, though the significance is marginal (0.482, 95% CI: 0.213 ~ 1.094, P-value: 0.081). The body could synthesize vitamin D from cholesterol in the skin with an adequate sun exposure. A four years consecutive study of vitamin D serum concentrations in CF patients reported that ranked per month, 25 (OH) D concentrations depicted a curve strikingly parallel to the amount of UVB exposure in the preceding months and a significant difference exists between 25 (OH) D concentrations in the 'Months with high UVB exposure' (May–October) and the 'Months with low UVB exposure' (November–April) same period. Those results indicated that 25 (OH) D concentrations clearly respond to the amount of sunshine in preceding months (Robberecht, Vandewalle et al. 2011). Another study reported that Summer levels of calcitriol in CF were significantly higher in Massachusetts than in Arizona; during winter, lower levels were found in Massachusetts than in Arizona which indicated a seasonal, sunlight-related influence on levels of vitamin D metabolites in patients with CF receiving approximately 1000 IU vitamin D per day (Reiter, Brugman et al. 1985).

Risk Factors for Vitamin D Deficiency in Generally healthy Group

In generally healthy group, 351 out 719 subjects have vitamin D deficiency (serum 25(OH)D less than 30 ng/mL). The unadjusted association analysis (univariate logistic/univariate association analysis) showed numerous factors affecting the risk for

develop vitamin D deficiency. However, after adjusted association analysis based on multivariable logistic regression, there are only 6 factors having an influence on serum vitamin D concentration including race, season, age, total body composition fat, intake of supplement vitamin D, moderate physical activity.

Similar to the result from CF group, race and season could be important factors influencing the serum concentration of vitamin D deficiency. For our healthy group, black people or African American have much higher risk to develop vitamin D deficiency than others (OR: 3.06, 95% CI: 1.92 ~ 4.88, P-value: < 0.001); vitamin D deficiency is less likely to be detected in season of summer and fall (higher opportunity to sun exposure). These findings were expected because of many prior studies (Reiter, Brugman et al. 1985, Tangpricha, Pearce et al. 2002, Weng, Shults et al. 2007, Cashman, Hill et al. 2008).

Total body fat mass measured by DXA showed a significant association with vitamin D deficiency in healthy subjects group. Prior studies in adults reported a strong association between hypovitaminosis D and obesity, in which fat mass was measured by whole-body DXA or bioelectrical impedance analysis (Looker 2005, Lucas, Bolland et al. 2005, Snijder, van Dam et al. 2005).This association is also showed in young adults and children (Kremer, Campbell et al. 2009, Kouda, Nakamura et al. 2013).

Taking moderate physical activity is also significantly and negatively associated with vitamin D deficiency which was reasonable and expected. Due to the body has the capability to synthesis the vitamin D with adequate sun exposure, the healthy people who take more physical activity could enjoy the outside activity more often and result in benefit the higher sun shine exposure. Taking physical activity may also suggest these

people pay more attention to their status of health, for example they could have more healthy daily diet which could contribute to increase vitamin D in serum.

There are two findings in healthy group not observed in CF group. One is supplement of vitamin D significantly decrease the risk to develop the vitamin D deficiency. As mentioned above, pancreatic insufficiency is quite often in CF patients which will induce a malabsorption of fat-soluble vitamins, such as A, E and D. It is more difficult to correct vitamin D concentration for CF patients with PI than healthy people. Many literatures have reported that supplement of vitamin D can decrease the risk of vitamin D deficiency in both healthy adults and children (Weaver and Fleet 2004, Gallagher, Sai et al. 2012). The other findings are that age showed a negative association with vitamin D deficiency in healthy group. Very few papers reported the relationship or trends between vitamin D deficiency and age in healthy people. Most papers focused on a narrow age range of their subjects which limited the capability to examine this association. In our current study, the age range of 719 healthy subjects is 18 to 82 and a significant negative association between age and vitamin D deficiency has been observed. However, a few literatures reported a negative association of vitamin D concentration with age during childhood and adolescence (Stein, Laing et al. 2006, Weng, Shults et al. 2007). This may be consequent from lack of consideration of confounders such as less outside activity in elder children. Two longitudinal studies have reported that the concentration of serum vitamin D vary with age in healthy older population. The result showed long-term serum 25-OHD levels remained fairly stable during aging with slightly increasing levels in people aged 55–65 years old and slightly decreasing levels in people aged 65–88 years old(Kozma Ahacic, Marti G. Parker et al. 2007, van Schoor, Knol et al. 2014). In our study, the physical

activity has been considered and the median age of health subjects is 49. The slightly negative association between age and vitamin D deficiency observed in our healthy subjects may be resulted in the slightly increasing adjustment of age on vitamin D concentration.

Risk Factors for the Combined Datasets (CF and Healthy Groups)

After combining CF patients and generally healthy people datasets only including the variables measured in both groups, the same statistical analyzes were performed. The findings are highly consistent with those in the above. Age, season, taking supplement vitamin D are negative associated with vitamin D deficiency, however, black race has a very strong positive association. Many prior studies have reported the status of cystic fibrosis will increase the risk to develop the vitamin D deficiency.

Based on the result of combine dataset, it shows disease of cystic fibrosis and the interaction of CF and BMI are significantly associated with vitamin D deficiency. In general, CF patients have higher risk to develop the vitamin D deficiency than the generally healthy people. Given that BMI is equal to 21.7 (mean of BMI in CF patients) and other variables are fixed, the estimated OR of the exposure to CF patients to the exposure to the generally healthy people is 2.3827 (95% CI: 1.3626 ~ 4.1666; p-value: 0.0023). The interaction of CF and BMI suggests that the association of BMI with vitamin D deficiency in CF patients is different from that in generally healthy people. For generally healthy people, higher BMI significantly increase the risk to develop vitamin D deficiency (OR with 1-unit increase of BMI: 1.1068; 95% CI: 1.0716 ~ 1.1432; p-value:

<0.0001). BMI is also significant when univariate analysis was applied to the analysis for generally healthy group, however, it was eliminated from final logistic model due to highly correlated with total body fat mass. So here, BMI may be confounded by total body mass which was not input into combined dataset.

However, for CF patients, increasing BMI in CF patients will not significantly alter the risk to develop the vitamin D deficiency (OR with 1-unit increase of BMI: 0.985; 95% CI: 0.8706 ~ 1.1147; p-value: 0.8118). This result is also observed in the analysis of CF patient dataset. In our study, mean of BMI in CF patients is significantly different from that in generally healthy people. The reason could be the high frequency of pancreatic insufficiency in CF patients resulting in malabsorbtion of diets. In this sense, higher BMI may indicate the less severity of pancreatic insufficiency of CF patients and therefore benefit those patients.

Limitations

There are several limitations in this study. Firstly, it is limited by a small sample size in CF patients group that may have contributed to restrict our inability to draw statistically significant conclusions with $\alpha = 0.05$ about the association of season with vitamin D deficiency for CF group. Fortunately, CF dataset still provided the marginal significance between those. Secondly, the information about CF patients is very limited. Lack of some important factors, such as total body fat, physical activity and reported history of other diseases et al, restrict our capability to target the risk factors in a comprehensive scale for CF patients. Thirdly, the comparison results observed from the

combine dataset is not very strong due to the difference between CF patients and generally healthy people samples. A case-control study with matching the demographic information will be more appropriate to address the question whether the risk factors, such as season, disease history, medicine/supplement intake, are different for CF patients and generally healthy people. However, it is difficult for this study to match those two samples based on age and race which indicates the demographic characteristics could be much different in our CF patients and healthy people.

7. Conclusion

In this study, we explore and compare the risk factors of vitamin D deficiency in CF patients and generally healthy population. Season with more sun exposure and non-black race will decrease the risk for vitamin D deficiency. For healthy people, taking supplement vitamin D, exercising more physical activity and less total body fat mass will contribute to lower the risk to develop vitamin D deficiency. However, we do not observe the significant association of vitamin D deficiency with supplement D intake and BMI in CF patients. It is interesting that age has a negative association with vitamin D deficiency in healthy group, which should be explored by further studies.

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Appendix I:

Table 1. Descriptive Analysis for Characteristics of CF Patients

Variable	Level	N = 95	%
Vitamin D deficiency	No	46	48.4
	Yes	49	51.6
Sex	Male	52	54.7
	Female	43	45.3
Race	Other	90	94.7
	Black or AA	5	5.3
Season	Spring or Winter	46	48.4
	Summer or Fall	49	51.6
Gene	hetero delta 508	42	44.2
	homo delta 508	53	55.8
Pancreatic insufficiency	No	4	4.2
	Yes	91	95.8
Supplement D	No	1	1.1
	Yes	94	98.9
Age	Mean	30.53	-
	Median	28	-
	Minimum	19	-
	Maximum	62	-

	Std Dev	10.26	-
	Missing	0	-
BMI	Mean	22.10	-
	Median	21.70	-
	Minimum	14.70	-
	Maximum	30.10	-
	Std Dev	3.37	-
	Missing	0	-

Table 2. Univariate Association with Vitamin D Deficiency in CF Patients

			Vitamin D Deficiency=Yes		
Covariate	**Statistics**	**Level**	**No N=46**	**Yes N=49**	**P-value***
Sex	N (Col %)	Male	29 (63.04)	23 (46.94)	0.115
	N (Col %)	Female	17 (36.96)	26 (53.06)	
Race	N (Col %)	Other	46 (100)	44 (89.8)	**0.026**
	N (Col %)	Black or AA	0 (0)	5 (10.2)	
Season	N (Col %)	Spring or Winter	18 (39.13)	28 (57.14)	0.079
	N (Col %)	Summer or Fall	28 (60.87)	21 (42.86)	
Gene	N (Col %)	hetero delta 508	23 (50)	19 (38.78)	0.271
	N (Col %)	homo delta 508	23 (50)	30 (61.22)	
Pancreatic insufficiency	N (Col %)	No	2 (4.35)	2 (4.08)	0.949
	N (Col %)	Yes	44 (95.65)	47 (95.92)	
Supplement D	N (Col %)	No	1 (2.17)	0 (0)	0.299
	N (Col %)	Yes	45 (97.83)	49 (100)	
Age	N		46	49	0.909
	Mean		30.65	30.41	
	Median		28.5	28	

			Vitamin D Deficiency=Yes		
Covariate	**Statistics**	**Level**	**No N=46**	**Yes N=49**	**P-value***
	N		46	49	
BMI	Mean		22.26	21.95	0.663
	Median		22.45	21.5	

Table 3. Univariate Logistic Regression Analysis in CF Patients

			Vitamin D Deficiency = Yes				
Covariate	**Level**	**N**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Sex	Male	52	0.519	0.228	1.178	0.117	0.117
	Female	43	-	-	-	-	
Race	Black or AA	5	>999.999	<0.001	>999.999	0.968	0.968
	Other	90	-	-	-	-	
Season	Summer or Fall	49	0.482	0.213	1.094	0.081	0.081
	Spring or Winter	46	-	-	-	-	
Gene	hetero delta 508	42	0.633	0.280	1.431	0.272	0.272
	homo delta 508	53	-	-	-	-	
Pancreatic insufficiency	No	4	0.936	0.126	6.935	0.948	0.948
	Yes	91	-	-	-	-	
Supplement D	No	1	0.000	0.000	I	0.986	0.986
	Yes	94	-	-	-	-	
Age		95	0.998	0.959	1.038	0.907	0.907
BMI		95	0.973	0.863	1.098	0.660	0.660

Table 4. Multivariate Logistic Regression Analysis in CF Patients

		Vitamin D Deficiency=Yes				
Covariate	**Level**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Season	Summer or Fall	0.54	0.23	1.24	0.144	0.144
	Spring or Winter	-	-	-	-	
Race	Black or AA	470940.19	0.00	1.41E284	0.968	0.968
	Other	-	-	-	-	

* Number of observations in the original data set = 95.
Number of observations used = 95.

Table 5. Descriptive Analysis for Characteristics of Generally Healthy People

Variable	Level	N = 719	%
Vitamin D deficiency	No	368	51.2
	Yes	351	48.8
Sex	Male	249	35.0
	Female	462	65.0
	Missing	8	-
Race	Other	550	77.5
	Black or AA	160	22.5
	Missing	9	-
Season	Spring or Winter	336	48.0
	Summer or Fall	364	52.0
	Missing	19	-
Cohabitants	Single	127	19.3
	Multiple	530	80.7
	Missing	62	-
Number of children	0	264	50.1
	1 ~ 2	191	36.2
	>2	72	13.7
	Missing	192	-

Variable	Level	N = 719	%
Income	<100 k	288	43.3
	100 k ~150 k	148	22.3
	>150 k	229	34.4
	Missing	54	-
Marital_status	Single	161	23.7
	Married	424	62.4
	Divorce/widow	95	14.0
	Missing	39	-
Education	Grade < 16	307	42.7
	Grade >= 16	412	57.3
Supplement D	No	370	51.5
	Yes	349	48.5
Supplement Calcium	No	559	77.7
	Yes	160	22.3
Ethnic	Not hispanic or Latino	701	98.7
	Hispanic or Latino	9	1.3
	Missing	9	-
Moderate physical activity	No	504	75.6
	Yes	163	24.4
	Missing	52	-

Variable	Level	N = 719	%
Vigorous physical activity	No	511	76.6
	Yes	156	23.4
	Missing	52	-
Current tobacco use	No	639	94.5
	Yes	37	5.5
	Missing	43	-
Reported history of diabetes	No	644	94.6
	Yes	37	5.4
	Missing	38	-
Reported history of hypertension	No	548	80.5
	Yes	133	19.5
	Missing	38	-
Reported history of hyperlipidemia	No	558	81.9
	Yes	123	18.1
	Missing	38	-
Taking blood pressure/glucose/lipid lowering drug	No	359	63.9
	Yes	203	36.1
	Missing	157	-
Taking blood pressure-lowering med	No	422	75.1
	Yes	140	24.9
	Missing	157	-

Variable	Level	N = 719	%
Taking any cholesterol-lowering medicine	No	448	79.7
	Yes	114	20.3
	Missing	157	-
Taking any glucose-lowering medicine	No	529	94.1
	Yes	33	5.9
	Missing	157	-
Multi-Vitamin intake	No	336	59.8
	Yes	226	40.2
	Missing	157	-
Age	Mean	48.00	-
	Median	49	-
	Minimum	18	-
	Maximum	82	-
	Std Dev	11.10	-
	Missing	13	-
BMI	Mean	27.84	-
	Median	26.55	-
	Minimum	16.60	-
	Maximum	59.20	-
	Std Dev	6.40	-
	Missing	15	-

Variable	Level	N = 719	%
Height in meter	Mean	1.69	-
	Median	1.69	-
	Minimum	1.47	-
	Maximum	1.97	-
	Std Dev	0.091	-
	Missing	15	-
weight in kg	Mean	79.68	-
	Median	77.14	-
	Minimum	43.55	-
	Maximum	184	-
	Std Dev	19.69	-
	Missing	15	-
Waist in inch	Mean	87.76	-
	Median	86.25	-
	Minimum	0.96	-
	Maximum	159	-
	Std Dev	15.70	-
	Missing	34	-
Waist to hip ratio	Mean	0.82	-
	Median	0.82	-
	Minimum	0.61	-
	Maximum	1.12	-
	Std Dev	0.086	-
	Missing	34	-

Variable	Level	N = 719	%
Total composition region fat	Mean	35.88	-
	Median	36.30	-
	Minimum	10.90	-
	Maximum	58.50	-
	Std Dev	8.86	-
	Missing	34	-
Total body total composition BMC in LB	Mean	5.93	-
	Median	5.75	-
	Minimum	3.44	-
	Maximum	11.20	-
	Std Dev	1.21	-
	Missing	49	-
Total body total BMD in g/cm2	Mean	1.20	-
	Median	1.19	-
	Minimum	0.80	-
	Maximum	1.71	-
	Std Dev	0.14	-
	Missing	36	-
Total body total composition fat	Mean	64.50	-
	Median	58.89	-
	Minimum	14.04	-
	Maximum	218	-
	Std Dev	28.22	-
	Missing	47	-

Table 6. Univariate Association with Vitamin D Deficiency in Generally Healthy People

			Vitamin D deficiency		
Covariate	**Statistics**	**Level**	**No N=368**	**Yes N=351**	**P-value**
sex	N (Col %)	Male	140 (38.67)	109 (31.23)	**0.038**
	N (Col %)	Female	222 (61.33)	240 (68.77)	
Race	N (Col %)	Other	320 (88.64)	230 (65.9)	**<.001**
	N (Col %)	Black or AA	41 (11.36)	119 (34.1)	
Season	N (Col %)	Spring or Winter	161 (45.35)	175 (50.72)	0.155
	N (Col %)	Summer or Fall	194 (54.65)	170 (49.28)	
Cohabitants	N (Col %)	Single	63 (19.21)	64 (19.45)	0.936
	N (Col %)	Multiple	265 (80.79)	265 (80.55)	
Number of children	N (Col %)	0	114 (48.31)	150 (51.55)	0.756
	N (Col %)	1~2	89 (37.71)	102 (35.05)	
	N (Col %)	>2	33 (13.98)	39 (13.4)	
income	N (Col %)	<100 k	129 (38.97)	159 (47.6)	0.063
	N (Col %)	100k ~ 150k	76 (22.96)	72 (21.56)	
	N (Col %)	>150k	126 (38.07)	103 (30.84)	
Marital_status	N (Col %)	Single	67 (19.76)	94 (27.57)	0.055
	N (Col %)	Married	221 (65.19)	203 (59.53)	
	N (Col %)	Divorce/widow	51 (15.04)	44 (12.9)	
Education	N (Col %)	Grade < 16	152 (41.3)	155 (44.16)	0.439
	N (Col %)	Grade > =16	216 (58.7)	196 (55.84)	

			Vitamin D deficiency		
Covariate	**Statistics**	**Level**	**No N=368**	**Yes N=351**	**P-value**
Supplement D	N (Col %)	No	154 (41.85)	216 (61.54)	**<.001**
	N (Col %)	Yes	214 (58.15)	135 (38.46)	
Supplement Calcium	N (Col %)	No	266 (72.28)	293 (83.48)	**<.001**
	N (Col %)	Yes	102 (27.72)	58 (16.52)	
ETHNIC	N (Col %)	Not hispanic or Latino	358 (99.17)	343 (98.28)	0.290
	N (Col %)	Hispanic or Latino	3 (0.83)	6 (1.72)	
Moderate physical activity	N (Col %)	No	235 (71.65)	269 (79.35)	**0.021**
	N (Col %)	Yes	93 (28.35)	70 (20.65)	
Vigorous physical activity	N (Col %)	No	234 (71.34)	277 (81.71)	**0.002**
	N (Col %)	Yes	94 (28.66)	62 (18.29)	
Current tobacco use	N (Col %)	No	330 (96.49)	309 (92.51)	**0.023**
	N (Col %)	Yes	12 (3.51)	25 (7.49)	
Reported history of diabetes	N (Col %)	No	334 (96.53)	310 (92.54)	**0.022**
	N (Col %)	Yes	12 (3.47)	25 (7.46)	
Reported history of hypertension	N (Col %)	No	293 (84.68)	255 (76.12)	**0.005**
	N (Col %)	Yes	53 (15.32)	80 (23.88)	
Reported history of hyperlipidemia	N (Col %)	No	287 (82.95)	271 (80.9)	0.486
	N (Col %)	Yes	59 (17.05)	64 (19.1)	

			Vitamin D deficiency		
Covariate	**Statistics**	**Level**	**No N=368**	**Yes N=351**	**P-value**
Taking any blood pressure/glucose/lipid lowering drug	N (Col %)	No	212 (70.2)	147 (56.54)	**<.001**
	N (Col %)	Yes	90 (29.8)	113 (43.46)	
Taking blood pressure-lowering med	N (Col %)	No	248 (82.12)	174 (66.92)	**<.001**
	N (Col %)	Yes	54 (17.88)	86 (33.08)	
Taking any cholesterol-lowering med	N (Col %)	No	239 (79.14)	209 (80.38)	0.714
	N (Col %)	Yes	63 (20.86)	51 (19.62)	
Taking any glucose-lowering med	N (Col %)	No	294 (97.35)	235 (90.38)	**<.001**
	N (Col %)	Yes	8 (2.65)	25 (9.62)	
Multi-Vitamin intake	N (Col %)	No	158 (52.32)	178 (68.46)	**<.001**
	N (Col %)	Yes	144 (47.68)	82 (31.54)	
Age	N		359	347	**0.003**
	Mean		49.23	46.74	
	Median		51	47	
BMI	N		360	344	**<.001**
	Mean		25.98	29.79	
	Median		25.45	28.2	

			Vitamin D deficiency		
Covariate	**Statistics**	**Level**	**No N=368**	**Yes N=351**	**P-value**
Height in Meter	N		360	344	0.141
	Mean		1.69	1.68	
	Median		1.69	1.68	
weight in kg	N		360	344	**<.001**
	Mean		74.96	84.63	
	Median		73.45	82.14	
Waist	N		348	337	**<.001**
	Mean		84.55	91.07	
	Median		83.55	90.45	
waist to hip ratio	N		348	337	0.109
	Mean		0.82	0.83	
	Median		0.81	0.83	
Total Composition Region Fat	N		353	332	**<.001**
	Mean		33.61	38.28	
	Median		33.1	38.5	
Total body total BMC in LB	N		343	327	0.365
	Mean		5.89	5.97	
	Median		5.67	5.86	
Total body BMD in g/cm2	N		351	332	**0.031**
	Mean		1.19	1.21	
	Median		1.18	1.2	

			Vitamin D deficiency		
Covariate	**Statistics**	**Level**	**No N=368**	**Yes N=351**	**P-value**
Total body total composition fat	N		344	328	**<.001**
	Mean		56.19	73.21	
	Median		53.01	67.2	

Table 7. Univariate Logistic Regression Analysis in Generally Healthy People

			Vitamin D deficiency = Yes				
Covariate	**Level**	**N**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Sex	Male	249	0.720	0.528	0.982	**0.038**	**0.038**
	Female	462	-	-	-	-	
Race	Black or AA	160	4.038	2.725	5.984	**<.001**	**<.001**
	Other	550	-	-	-	-	
Season	Summer or Fall	364	0.806	0.599	1.085	0.155	0.155
	Spring or Winter	336	-	-	-	-	
Cohabitants	Single	127	1.016	0.690	1.496	0.936	0.936
	Multiple	530	-	-	-	-	
Number of children	0	264	1.113	0.660	1.880	0.688	0.756
	1~ 2	191	0.970	0.563	1.670	0.912	
	>2	72	-	-	-	-	
Income	< 100k	288	1.508	1.064	2.137	**0.021**	0.064
	100 ~150 k	148	1.159	0.766	1.754	0.485	
	>150k	229	-	-	-	-	
Marital status	Single	161	1.626	0.976	2.710	0.062	0.056
	Married	424	1.065	0.682	1.663	0.783	
	Divorce/widow	95	-	-	-	-	

			Vitamin D deficiency = Yes				
Covariate	**Level**	**N**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Education	Grade <16	307	1.124	0.836	1.510	0.439	0.439
	Grade > =16	412	-	-	-	-	
Supplement D	No	370	2.223	1.649	2.997	**<.001**	**<.001**
	Yes	349	-	-	-	-	
Supplement Calcium	No	559	1.937	1.348	2.784	**<.001**	**<.001**
	Yes	160	-	-	-	-	
Ethnic	Not hispanic or Latino	701	0.479	0.119	1.931	0.301	0.301
	Hispanic or Latino	9	-	-	-	-	
Moderate physical activity	No	504	1.521	1.065	2.171	**0.021**	**0.021**
	Yes	163	-	-	-	-	
Vigorous physical activity	No	511	1.795	1.246	2.585	**0.002**	**0.002**
	Yes	156	-	-	-	-	
Current tobacco use	No	639	0.450	0.222	0.910	**0.026**	**0.026**
	Yes	37	-	-	-	-	
Reported history of diabetes	No	644	0.446	0.220	0.902	**0.025**	**0.025**
	Yes	37	-	-	-	-	
Reported history of hypertension	No	548	0.577	0.392	0.848	**0.005**	**0.005**
	Yes	133	-	-	-	-	

			Vitamin D deficiency = Yes				
Covariate	**Level**	**N**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Reported history of hyperlipidemia	No	558	0.871	0.589	1.287	0.487	0.487
	Yes	123	-	-	-	-	
Taking any blood pressure/glucose /lipid lowering drug	No	359	0.552	0.390	0.782	**<.001**	**<.001**
	Yes	203	-	-	-	-	
Taking blood pressure-lowering med	No	422	0.441	0.298	0.652	**<.001**	**<.001**
	Yes	140	-	-	-	-	
Taking any cholesterol-lowering med	No	448	1.080	0.714	1.633	0.715	0.715
	Yes	114	-	-	-	-	
Taking any glucose-lowering med	No	529	0.256	0.113	0.578	**0.001**	**0.001**
	Yes	33	-	-	-	-	
Multi-Vitamin intake	No	336	1.978	1.400	2.795	**<.001**	**<.001**
	Yes	226	-	-	-	-	
Age		706	0.980	0.967	0.993	**0.003**	**0.003**
BMI		704	1.119	1.086	1.152	**<.001**	**<.001**
Height in meter		704	0.293	0.057	1.504	0.141	0.141
Weight in kg		704	1.028	1.019	1.037	**<.001**	**<.001**

			Vitamin D deficiency = Yes				
Covariate	**Level**	**N**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Waist		685	1.029	1.018	1.040	**<.001**	**<.001**
Waist to hip ratio		685	4.178	0.726	24.036	0.109	0.109
Total Composition Region Fat		685	1.065	1.046	1.085	**<.001**	**<.001**
Total body total BMC in LB		670	1.060	0.935	1.201	0.365	0.365
Total body total BMD in g/cm2		683	3.403	1.115	10.389	**0.031**	**0.031**
Total body total composition fat		672	1.026	1.019	1.033	**<.001**	**<.001**

Table 8 Multivariate Logistic Regression Analysis in Generally Healthy People

		Vitamin D deficiency = Yes				
Covariate	**Level**	**Odds Ratio**	**95%CI Low**	**95%CI Up**	**OR P-value**	**Type3 P-value**
Season	Summer or Fall	0.69	0.49	0.98	**0.041**	**0.041**
Race	Black or AA	2.88	1.83	4.53	**<.001**	**<.001**
Supplement_D	Yes	0.46	0.32	0.65	**<.001**	**<.001**
Moderate physical activity	Yes	0.58	0.38	0.88	**0.010**	**0.010**
Age		0.97	0.95	0.99	**<.001**	**<.001**
Total body total composition fat		1.02	1.02	1.03	**<.001**	**<.001**

* Number of observations in the original data set = 719. Number of observations used = 634.

Table 9 Coefficient Estimate for Multivariate Logistic Regression for Generally Healthy People

		Vitamin D deficiency = Yes			
Parameter	**Level**	**Estimate**	**Standard error**	**Chi-Square**	**Pr > ChiSq**
Intercept		0.4171	0.4588	0.8262	0.3634
Season	Summer or Fall	-0.3674	0.1797	4.1786	0.0409
Race	Black or AA	1.0568	0.2313	20.8787	<.0001
Supplement_D	Yes	-0.781	0.1783	19.1931	<.0001
Moderate physical activity	Yes	-0.5444	0.2109	6.6645	0.0098
Age		-0.0308	0.00845	13.2853	0.0003
Total body total fat		0.0246	0.00386	40.5278	<.0001

Table 10 Coefficient Estimate for Multivariate Logistic Regression for the Combine Dataset

		Vitamin D deficiency = Yes			
Parameter	**Level**	**Estimate**	**Standard error**	**Chi-Square**	**Pr > Chi Sq**
Intercept		-1.4516	0.5287	7.5378	0.006
CF	Yes	3.3965	1.4868	5.2184	0.0223
BMI		0.1015	0.0165	37.8518	<.0001
Age		-0.0216	0.00722	8.937	0.0028
Season	Summer or Fall	-0.4079	0.157	6.7468	0.0094
Race	Black or AA	1.1349	0.2182	27.0493	<.0001
Supplement D	Yes	-0.7433	0.1679	19.5906	<.0001
CF * BMI		-0.1165	0.0648	3.2371	0.072

Appendix II :

```
proc datasets lib=d memtype=data;
modify normf;
attrib _all_ format=;
attrib _all_ label="";
run;


proc prints data=d.normf (obs=50);
run;

proc format;

value sex  1="Female"
           0="Male";

value do 1="Yes"
         0="No";

value Ethnic 1="Hispanic or Latino"
             0="Not hispanic or Latino";

value gene 1= "hetero delta 508"
           2="homo delta 508"
           0="Other";
Value race 1="Black or AA"
           0="Other";
value season 1="Sun_high"
             0="Sun_low";
value co_hab 0="Alone"
             1="Live with others";
value child_nbr 0="No child"
                1="live with 1 or 2 persons"
                     2="live with many people";
value income 0="<100 k"
             1="100 k =< and =<150 k"
                  2=">150 k";
value m_Status 0="single"
               1="married"
                   2="divorce or widow";
value education 0="Grade < 16"
                1="Grade > 16";
value Ethnic 1="Hispanic or Latino"
             0="Not hispanic or Latino";

run;

data nd.norm (keep= id cf vitD_def age bmi sex race season co_hab
child_nbr income marital_status Education Supplement_D
```

```
Supplement_Ca ht_m wt_kg waist whr totregPFAt Totbmc totbmd
totfatmass ethnic caps_modguide caps_vigguide tobuse hx_dm hx_htn
hx_chol Med bpmed chol_med glu_med MVI1 );
   set d.normf(rename=(cf=cf1 vitD_def=Vitd_def1 race=race1
season=season1 co_hab=co_hab1 child_nbr=child_nbr1
income_level=income1 Marital_status=Marital_status1
Education=Education1));
   if cf1="Yes" then CF=1;
      else if cf1="No" then CF=0;
   if VitD_def1="Yes" then VitD_def=1;
      else if VitD_def1="No" then VitD_def=0;
   if race1="Black or AA" then Race=1;
      else if race1="Other" then Race=0;
   if season1="SUN_Y" then Season=1;
      else if season1="SUN_N" then Season=0;
   if Supple_D="Yes" then Supplement_D=1;
      else if Supple_D="No" then Supplement_D=0;
   if Supple_ca="Yes" then Supplement_Ca=1;
      else if Supple_Ca="No" then Supplement_Ca=0;
   if co_hab1="relative" then co_hab=1;
      else if co_hab1="Alone" then co_hab=0;
   if child_nbr1="No child" then child_nbr=0;
      else if child_nbr1="1 or 2" then child_nbr=1;
            else if child_nbr1="Many" then child_nbr=2;
   if income1="<100k" then income=0;
      else if income1="100~150k" then income=1;
            else if income1=">150k" then income=2;
   if Marital_status1="Single" then Marital_status=0;
      else if Marital_status1="Married" then Marital_status=1;
            else if marital_status1="Divorce/Widow" then
Marital_status=2;
     if Education1="Grade < 16" then Education=0;
       else if Education1="Grade > 16" then Education=1;

    format cf Vitd_def Supplement_D Supplement_Ca caps_modguide
caps_vigguide tobuse hx_dm hx_htn hx_chol Med bpmed chol_med
glu_med MVI1 do.
          sex sex. race race. season season. Ethnic Ethnic. ;
    label co_hab="Cohabitants"
           child_nbr="Number of children"
             ht_m="Height in Meter"
             wt_kg="weight in kg"
             WHR="waist to hip ratio"
          totregPFAt="Total Composition Region Fat"
          totfatmass="Total bodytotal composition fat"
          caps_modguide="Moderate physical activity"
          caps_vigguide="Vigorous physical activity"
          tobuse="Current tobacco use"
          hx_dm="Reported history of diabetes"
          hx_htn="Reported history of hypertension"
          hx_chol="Reported history of hyperlipidemia"
```

```
          Med="Taking any blood pressure/glucose/lipid lowering
drug"
          bpmed="Taking blood pressure-lowering med"
          chol_med="Taking any cholesterol-lowering med"
          glu_med="Taking any glucose-lowering med"
          MVI1="Multi-Vitamin intake";

run;

data temp;
  set nd.norm;
  keep id cf vitd_def race season sex age bmi supplement_D;
run;


data nd.combine;
  set nd.cf(drop=gene pancreatic_insuff) temp;
run;


TITLE 'Table Univariate Association with Vitamin D Deficiency for
whole population';
%UNI_CAT(dataset =  nd.combine,
      outcome = VitD_def,
      clist = cf sex race season Supplement_D,
      nlist = age bmi ,
      nonpar = T,
      rowpercent = F,
      orientation = portrait,
      outpath = C:\Users\thesis\report\,
      fname = Table 6 Univariate Association with Vitamin D
Deficiency for whole population);
TITLE;

proc logistic data=nd.combine;
class cf sex race season supplement_D;
model vitd_def (event="Yes")=cf sex race season Supplement_D age
bmi cf*sex cf*race cf*season cf*supplement_D
                              /selection=stepwise slentry=0.1
slstary=0.1 details lackfit;
                                        run;

proc logistic data=nd.combine;
class cf race season supplement_D;
model vitd_def (event="Yes")=cf race season Supplement_D age
bmi/lackfit;
                                        run;

%include "C:\Users\thesis\Macros\Macros\DESCRIPTIVE V10.sas";
%include "C:\Users\thesis\Macros\Macros\UNI_CAT V28.sas";
%include "C:\Users\thesis\Macros\Macros\UNI_LOGREG V12.sas";
%include "C:\Users\thesis\Macros\Macros\MULTIPLE_LOGREG V12.sas";
```

```
%include "C:\Users\thesis\Macros\Macros\LOGREG_SEL V11.sas";


Title "Table 5 Descriptive Statistics for Characteristics of Non-
CF Patients";
%DESCRIPTIVE(dataset = nd.norm,
      clist = VitD_def sex race season co_hab child_nbr income
marital_status Education Supplement_D Supplement_Ca ethnic
caps_modguide caps_vigguide tobuse hx_dm hx_htn hx_chol Med bpmed
chol_med glu_med MVI1 ,
      nlist = age bmi ht_m wt_kg waist whr totregPFAt Totbmc
totbmd totfatmass,
      outpath =C:\Users\thesis\report\,
      fname = Table 5 Descriptive Statistics for Characteristics
of Non-CF Patients);
TITLE;

TITLE 'Table 6 Univariate Association with Vitamin D Deficiency
in Non-CF patients';
%UNI_CAT(dataset =  nd.norm,
      outcome = VitD_def,
      clist =  sex race season co_hab child_nbr income
marital_status Education Supplement_D Supplement_Ca ethnic
caps_modguide caps_vigguide tobuse hx_dm hx_htn hx_chol Med bpmed
chol_med glu_med MVI1,
      nlist = age bmi ht_m wt_kg waist whr totregPFAt Totbmc
totbmd totfatmass,
      nonpar = T,
      rowpercent = F,
      orientation = portrait,
      outpath = C:\Users\thesis\report\,
      fname = Table 6 Univariate Association with Vitamin D
Deficiency in Non-CF patients);
TITLE;

TITLE 'Table 7 Univariate Logistic Regression in Non-CF Patients';
%UNI_LOGREG (DATASET = nd.norm,
     OUTCOME = VitD_def,
     EVENT =' Yes',
     CLIST = sex race season co_hab child_nbr income
marital_status Education Supplement_D Supplement_Ca ethnic
caps_modguide caps_vigguide tobuse hx_dm hx_htn hx_chol Med bpmed
chol_med glu_med MVI1,
     NLIST = age bmi ht_m wt_kg waist whr totregPFAt Totbmc
totbmd totfatmass,
     OUTPATH= C:\Users\thesis\report\,
     FNAME = Table 7 Univariate Logistic Regression in Non-CF
Patients,
     ORIENTATION = portrait, DEBUG=F);
TITLE;
proc print data=nd.norm (obs=10);
run;
```

```
TITLE 'Table 9-1 Mutivariate Logistic Regression in Non-CF
patients';
ODS OUTPUT NObs = nobs Type3 = type3 ParameterEstimates =
estimate CLparmWald = CI ModelInfo=modelinf ResponseProfile=resp;
PROC LOGISTIC data = nd.norm;
   class season race Supplement_D caps_modguide/param=glm;
   model vitd_def(event="Yes") =age waist whr totfatmass season
race Supplement_D  caps_modguide /CLPARM=wald ;
run;

%multiple_logreg(event=Yes,
      outpath = C:\Users\thesis\report\,
      fname = Table 9-1 Mutivariate Logistic Regression in Non-CF
patients);
TITLE;
TITLE 'Table 8 Mutivariate Logistic Regression in Non-CF
patients';
%logreg_sel(dsn = nd.norm,
      outcome = vitD_def,
      event = 'Yes',
      var =  age bmi wt_kg waist whr totregPFAt  totbmd
totfatmass sex race season income marital_status Supplement_D
Supplement_Ca caps_modguide caps_vigguide tobuse hx_dm hx_htn Med
bpmed glu_med MVI1,
      cvar = sex race season income marital_status Supplement_D
Supplement_Ca caps_modguide caps_vigguide tobuse hx_dm hx_htn Med
bpmed glu_med MVI1,
      inc=1,
      slstay = .20,
      report = T,
      outpath = C:\Users\thesis\report\,
      filename = Table 8 Mutivariate Logistic Regression in Non-
CF patients);
TITLE;
```