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Trends in Prediabetes and Associated Comorbid Conditions in Adolescents Aged 12 to 19 Years, Between 2003 and 2014.

Taylor Dias

ABSTRACT

Trends in Prediabetes and Associated Comorbid Conditions in Adolescents Aged 12 to 19 Years, Between 2003 and 2014.

By

Taylor Patrice Dias

04/16/2018

NTRODUCTION: Understanding of the trends in Pre-Diabetes (PD), a reversible condition and precursor/risk factor for Type II Diabetes Mellitus (T2DM), among adolescents may help to develop robust public health initiatives for slowing the epidemic of T2DM and its associated comorbidities. Currently, published research only investigates only the prevalence of T2DM and T1DM in the adolescent population with no focus on PD. We have the following three hypotheses: the prevalence of PD will be increasing during the study period, the prevalence of both comorbid conditions will be increasing in prevalence, there association of PD with each of the comorbid conditions will grow stronger over the study period.

AIM: Our aim is to determine the prevalence of PD and associated comorbid conditions in the adolescent population. Slowing the progress of this epidemic is crucial for improving the long-term quality of life for high-risk populations, and can prevent adolescents from having expensive chronic conditions as they progress to adulthood.

METHODS: Data from NHANES 2003 - 2014 was used conduct analyses. The study sample was restricted to include only participants aged 12 to 19 years, and participants who were selected for lab work as this is the smallest subset of the participants for each year. Proper sample weights, according to sampling methodology were used, to obtain prevalence value for each year, as well as to obtain correlation values in SAS 9.4.

RESULTS & Discussion: Contrary to our hypotheses there was an observed decrease in prevalence of PD and LDL category as well as average LDL reading during the study period. Additionally, the associations of PD and the comorbid were weak, and showed no trend during the study period. However, the prevalence of overweightness/obesity remained constant during the study period, though the prevalence remained high.

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by

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APPROVAL PAGE

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Author's Statement Page

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Introduction

The prevalence of Type 2 Diabetes Mellitus (T2DM) has been rapidly increasing in the United States, and remains one of the top 10 causes of death in the United States. The American Diabetes Association (ADA) reported that there were 29.1 million cases of T2DM in 2015 in the American population. There has also been a dramatic increase in the prevalence of T2DM among adolescents, with and observed increase of 7.1% annually from 2002 to 2012(Mayer-Davis et al., 2017). As with most chronic diseases, the observed increase was the greatest in minority groups (i.e. Hispanics and African Americans) in the Unites States. The CDC cites the report by Dr. Mayer-Davis and her colleagues noting that there is not much understood about the rise in incidence of T2DM, nor has an explanation for the variances among genders and racial-ethnic groups been identified. It is crucial that we begin understanding the reasons for this growing epidemic, as the ADA currently reports it as the seventh leading cause of death in the United States. Diabetes could continue to develop into a major public health crisis if there is not more investigation into the risk factors associated with the epidemic.

There has been some research to investigate the clustering of metabolic syndromes across different racial ethnic groups. In 2014, Okosun,Annor, and colleagues found that the clustering of cardiometabolic risk factors is positively associated with elevated HbA1c. Okosun and his colleagues also noted that "the joint occurrence of abdominal obesity and high blood pressure were much more highly associated with elevated HbA1c ", lending more support to the concept that there needs to be more investigation into the comorbid conditions that are clustering together in the population. However, the target population of this research was not adolescents as will be in the present research, indicating there is a knowledge gap about the trends of metabolic conditions in adolescents in the American population. Several researchers have noted that there has been an epidemiologic shift in diabetes among the adolescent population, shifting from predominantly Type 1 Diabetes Mellitus (T1DM) to also including a high incidence of T2DM. Investigation into the origin or the epidemiologic shift have identified several behavioral changes that may have contributed to the shift in adolescents, including a more sedentary lifestyle and eating more calorie-dense, nutrient poor foods (Delahanty et al., 2013).

The recent epidemiologic shift in diabetes in adolescents is concerning for several reasons. The first is that the prevalence of comorbid conditions, such as hypertension and arterial stiffness, is higher among children with T2DM than T1DM. It has been observed that adolescents with T2DM had a higher prevalence of most comorbid conditions, and were disproportionally effected with 72% having at least one complication or comorbidity (Dabelea et al., 2017). Additionally, there has been minimal investigation into the effects that a longer burden of disease will have on the population. As more adolescents are being diagnosed with T2DM they will carry that burden into adulthood and throughout their lifetime. A longer burden of diseases could lead to increased mortality and morbidity, and the medical and capital cost on society will increase dramatically (ADA).

There's a paucity of research examining biological precursors to the development of Diabetes, in an attempt to understand the current epidemic. For example, by understanding of the trends in Pre-Diabetes (PD), a reversible condition and precursor/risk factor for T2DM, among adolescents may help to develop robust public health initiatives for slowing the epidemic of T2DM and its associated comorbidities. Currently, published research only investigates only the prevalence of T2DM and T1DM in the adolescent population with no focus on PD. Slowing the progress of this epidemic is crucial for improving the long-term quality of life for high-risk populations, and can prevent adolescents from having expensive chronic conditions as they progress to adulthood. There is currently a lack of research describing the trends of PD and associated comorbid conditions in adolescents, as the limited research available focuses on T2DM and T1DM. The present study aims to analyze the trends of PD and a two of the associated comorbid conditions based on data from National Health and Nutrition Examination Survey (NHANES). We have the following three hypotheses: the prevalence of PD will be increasing during the study period, the prevalence of both comorbid conditions, cholesterol status and BMI category,

will be increasing in prevalence as well, and the association of PFG with each of the comorbid conditions will grow stronger over the study period.

Methods and Procedures

2.1 Study Design

Data from the 2003 - 2014 NHANES (collected in two year increments) survey was used for analysis in the study. Each survey is composed of a cross-sectional sample taken from the non-institutionalized population in the United States, and is intended to be representative of the entire population. The survey is composed of both a self-reported survey that is administered to participants, as well as a subsample of participants who are selected for physical and laboratory examination. NHANES uses a complex sampling strategy ,which includes oversampling underrepresented populations to ensure that the sample is representative of the entire population. A detailed description of the sampling methodology can be found on the National Center for Health Statistics website.

2.2 Study Population

The study population was restricted to only include participants aged 12 to 19 years. The minimum age of 12 years was selected because it is the minimum age for which laboratory and examination data were collected. The dataset was further restricted in each year to only individuals who were selected for the laboratory examination. In the NAHNES sample for each year, a small subset was selected to go through a physical and laboratory examinations, in addition to the survey. The subset that was selected for the laboratory examination represents the smallest sub-sample, of the sample for each year. There were a total of 4,639 observations in the study, comprised of varying numbers of observations for each year.

2.3 Definition of Terms

Ranges for all conditions were adapted from the ranges listed by the Mayo Clinic, as they continue to be a leader in the biological research community, and were assigned to each participant using the raw data, biomarker value. Both PD and T2DM were defined using the plasmas fasting glucose (PFG) (mg/dL) reading for each participant, ideal PFG was defined as being less than 100 mg/dL, PD as greater than or equal to 100 mg/dL and less than or equal to 125 mg/dL, and T2DM as a reading of greater than 125 mg/dL. A body mass index (BMI) category was also assigned to each participant based on his/her reading: a reading of lower than 18.5 kg/m^2 was categorized underweight, greater than or equal to 18.5 kg/m^2 and less than or equal to 24.9 was categorized ideal, greater than or equal to 25 kg/m^2 and less than or equal to 29.9 kg/m^2 was categorized overweight, and a reading of 130 kg/m^2 or greater was categorized as obese. Additionally, each participant was assigned a cholesterol category based on their low-density lipoprotein (LDL) reading in mg/dL: a reading of 129 mg/dL or less was categorized as ideal, a reading greater than or equal to 130 mg/dL and less than or greater than or equal to 159 mg/dL as borderline, and a reading greater than or equal to 160 mg/dL as high.

2.4 Statistical Analysis

All analysis were completed using SAS 9.4 for windows. In order to account for the complex sampling technique and to ensure that the results are applicable to the United States population as intended the proper weight, strata, and cluster variables were used. The weight assigned to the lab data was used as the weight for analysis, since it is the smallest subset of the study sample. Weighted frequencies were used to obtain prevalence values for each condition, during each study year. Mean values for each biomarker were obtained using the variables LBXGLU (PFG), BXIBMI (BMI), and LBDLDL (LDL) for each participant each year. Additionally, 95% confidence intervals were obtained for the mean values for each biomarker at the beginning and end of the study to determine if the mean value has changed overtime. Pearson's correlations were conducted to look at the associations of the biomarkers over the study period.

Results

The prevalence of PD was generally trending downwards during the study period. In 2004 the PD prevalence was 9.95% with a peak of 27.39% seen in 2008 (Figure 1), by 2014 prevalence had dropped to 0% (according to the sample). Comparatively, the prevalence of adolescents having non-ideal LDL cholesterol levels remained relatively constant during the study period, though there was an overall decrease of 1.18% during the study period (Figure 2). The low prevalence each year was comprised mostly of adolescents who have a borderline LDL cholesterol level, and not those that are classified as high and very high. As seen in Figure 3, the prevalence of overweightness and obesity was trending upwards during the study period, with a peak prevalence in 2008 of 34.83% . It is also of note that the prevalence of obesity and overweightness as well as PD both peaked in 2008, as shown in figure 4 that combines the three previous figures to visualize how the three conditions trended simultaneously during the study period. The trend in raw BMI reading is parallel to the trend in prevalence of overweightness and obesity. Both were generally trending upwards, mean (95% CI) BMI at the start of the study was 23.74 kg/m^2 (23.03, 24.47) and at the end of study the mean BMI had increased to 24.19 kg/m^2 (23.24, 25.13).

Conversely to the accordance in trends between BMI category and mean BMI value, the trends in PD and LDL category display different trends that what was observed in the corresponding biomarker. Figures 5 displays the mean PFG value for the population during the study period, note that the trend in PFG differs from the trend in PD and is overall trending upwards. There was a sharp peak in 2008, followed by a steady increase the began in 2010. In 2004 the mean (95% CI) PFG was 91.01 mg/dL (89.76, 92.25) and by the end of the study period it was 94.22 mg/dL (92.71, 95.74).In contrast to what was observed in medically defined cholesterol category, mean LDL values decreased in the populations after a peak in 2010(figure 6). At the beginning of the study period the mean (95% CI) LDL was 90.46 mg/dL (88.34,92.58) and at the conclusion of the study period the mean value had dropped to 86.86 mg/dL (83.22, 90.49). Tables 1– 3 are frequency tables that give the frequency for each condition category (Diabetes, BMI, & Cholesterol), both weighted and unweighted frequencies are listed.

There were no strong associations between PFG and either of the other two biomarkers (LDL and BMI) during the study period. In 2010 there was a statistically significant ($p<.0001$) correlation between PFG and BMI the correlation coefficient remained near zero ($r=.22$) indicating a weak positive correlation. Correlation coefficients and p-values for each year are presented in Table 4.

Discussion

The purpose of this study was to determine the trends in PD in adolescents and determine if the trends are similar to the trends observed in T2DM. If more cases of PD can be identified in the population prevention efforts could be aimed at adolescent with PD who are likely at high-risk of developing T2DM. It is crucial to identify and treat adolescent before they develop T2DM, as once they have been diagnosed they cannot be cured. Again our three hypotheses were: the prevalence of PD will be increasing during the study period, the prevalence of both comorbid conditions, cholesterol status and BMI category, will be increasing in prevalence as well, and the association of PFG with each of the comorbid conditions will grow stronger over the study period.

The results of the study do not support our hypothesis that the prevalence of PD was increasing in the adolescent population between 2004-2014, in fact according to the NHANES data PD prevalence was trending downwards during this period. Though there was no increase in adolescents who would be clinically defined as having PD, the raw mean PFG values suggest that insulin resistance continued to increase in the population during the period, as indicated by upward shift of the 95% CI, with the only overlap observed at the upper confidence limit for 2004 and the lower confidence limit for 2014. This finding could be indicative of another possible peak in prevalence PD, similar to what was observed in the population in 2008, could occur again in the near future. The mean PFG value in 2014 was only 6

points below being classified clinically as PD, and it can be inferred that if PFG continues to trend upward the mean value could reach the clinical definition of PD in the coming years.

Our results also do not support the hypothesis that the prevalence of non-ideal cholesterol would be increasing during the study period. The prevalence of non-deal cholesterol remained low, and relatively constant with no significant variations during the study period. Upon reviewing the frequency table it can be observed that most cases are classified as borderline versus high or very high, which indicates that most participants are still only at risk and do not yet have a cholesterol problem. This is a good sign for the adolescent population, and indicative that the consumption of foods high in saturated fatty acids may not yet begun to have a widespread effect on cardiovascular health in this population. Mean LDL level also remained constant as can be determined by the large overlap of the confidence intervals for 2004 and 2014.

The prevalence of overweightness and obesity does not directly support hypothesis that conditions that are comorbid with PD was increasing in the adolescent population. However, the prevalence was high and relatively constant as the data indicates that approximately a third of the adolescent population was overweight or obese during the entire study period. This constant rate of obesity is further supported by the mean BMI at the begging and the end of the study period, and the large overlap in the confidence intervals for both values. Throughout the study period the mean BMI value remained near the threshold of overweight, and indicates that weight remains an issue in the adolescent population. Overweightness/obesity is a risk factor for T2DM and the high mean BMI values could be indicative that that the one of underlying problems that contributes to its diagnosis of PD still exists in the population at a high percentage. As previously mentioned the mean PFG also experienced a sharp peak in 2008, which could indicates that until the obesity prevalence declines to a lower percentage of the population we cannot infer that the Diabetes epidemic is under control. Additionally, the high prevalence of obesity indicates that the proposed causes of this epidemic (sedentary life-style and consuming mostly calorie-dense, low nutrient foods) may still be an underlying issues within this age group. This indicates, in contrast to PD prevalence results, that public health interventions aimed at behavioral changes may need to be intensified to reach more adolescents, and more robustly evaluated for their efficacy.

Over all the results do not fully support our hypothesis, and are dissimilar from the trends seen in adults and the limited research available in the adolescent populations. Previous studies have identified that metabolic conditions cluster together and often excess weight is associated with poor cardiovascular health which was not observed in the present study. Copeland et. al. outline several behavioral changes in the adolescent population, including eating consuming fast foods, snacking behaviors, and increased screen time, that are contributing to a "medical metamorphosis" in the populations. Their findings indicate that the T2DM is still a major concern among adolescents. The amount of negative behavioral changes (sedentary lifestyle and poor diet) and increasing prevalence of T2DM noted by the majority of research, though not supported by the findings of this research, indicates that the is a real public health crisis occurring in the United States adolescent population. T2D prevalence is rapidly increasing, and increased 7.1% annually over a time period that was almost concurrent with the present study period Mayer-Davis et al., 2017). This indicats that there need to be more research into the prevalnce of PD, as adolescents must first have PD before T2DM. If we can identfity these adolescetns earlier, we may be able to implent more effective interventions and slow or stop the progressions of the disease.

Limitations

There are significant limitations to our analysis, which can provide an explanation for why the trends observed in the present research are dissimilar for the trends previously observed in the population. Though NHANES is intended to be representative of the populations our sample was so heavily restricted that it was no longer representative. Additionally, the selected biomarkers may not have been sensitive enough as persons currently taking medications to control diabetes of cholesterol may have been included in the sample. Sample sizes varied each year, though weighted, and make it difficult to observe the trends.

Our results provide support for the funding of better surveillance of the adolescent population on a large scale similar to NHANES. These results demonstrate that it can be difficult to analyze trends in this population when there is not adequate surveillance data, or resources to complete data collection. Future research should aim to use a data source that only contains adolescents who are not being treated, and have not been diagnosed, or collect a new representative sample.

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Appendix

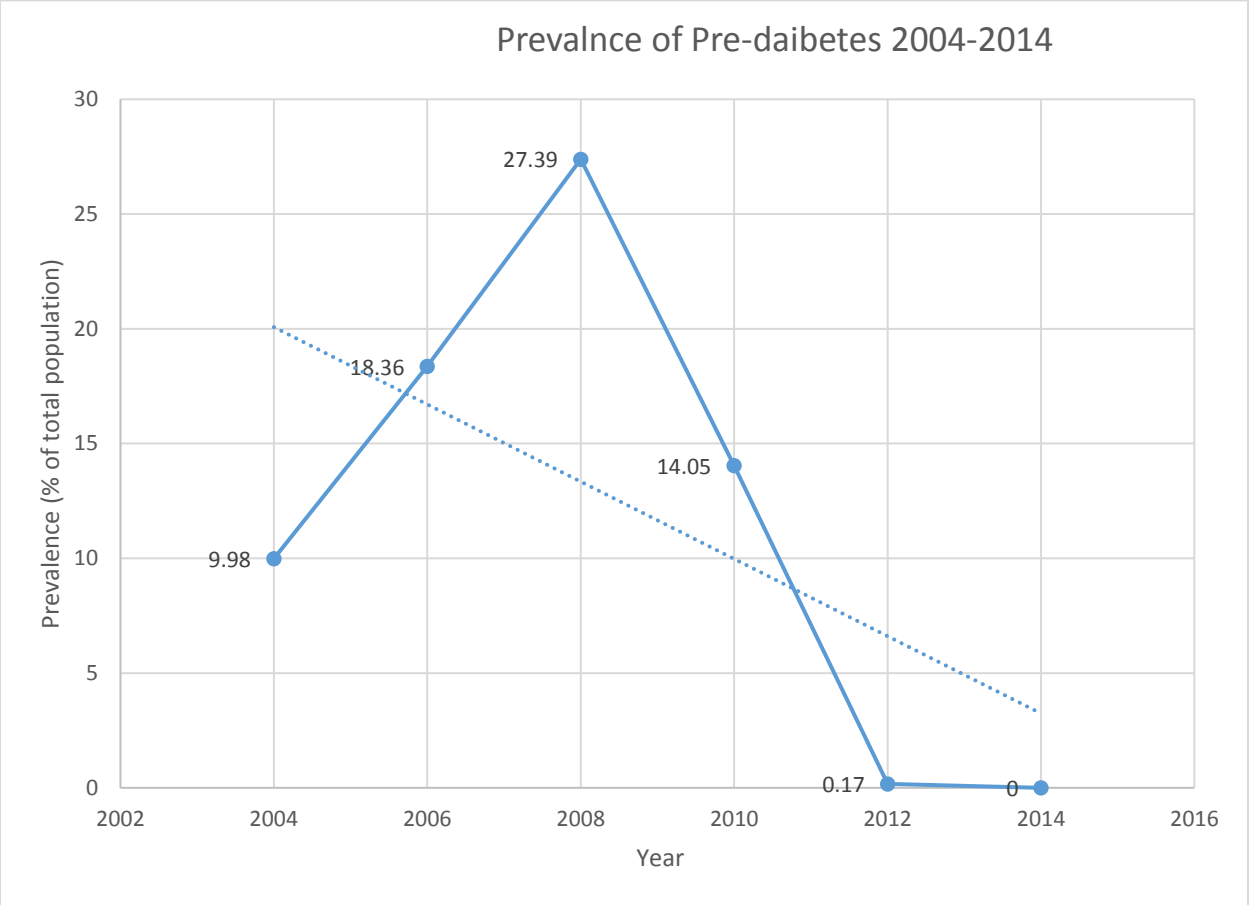

Figure 1: Trend in prevalence pre-diabetes during the study period of 2004-2014. Prevalence was derived from the weighted frequencies of each year. The dashed line represents the linear trend during the time period.

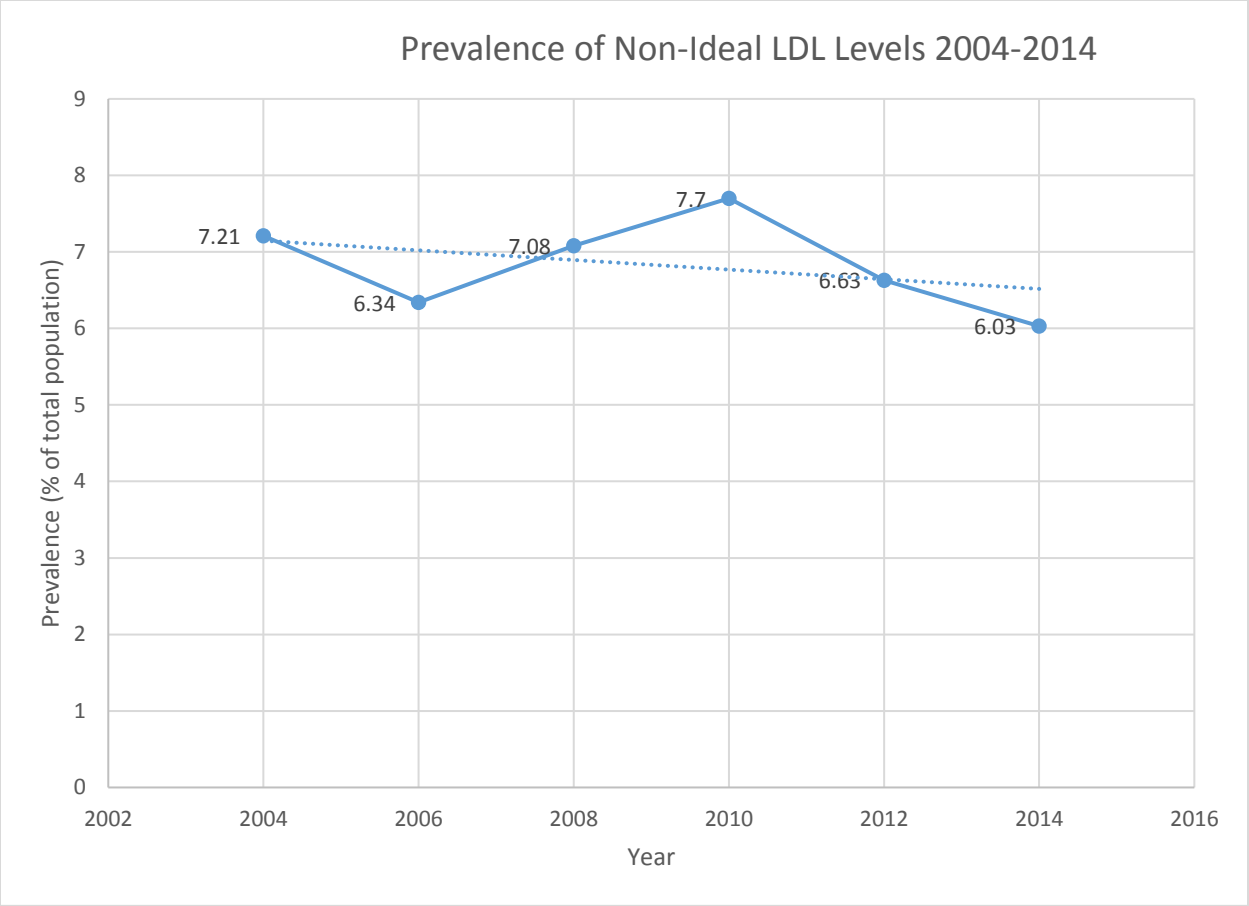

Figure 2: Trend in prevalence LDL levels that are above ideal (borderline, high and very high) during the study period of 2004-2014. Prevalence was derived from the combined weighted frequencies of each category, for each year. The dashed line represents the linear trend during the time period.

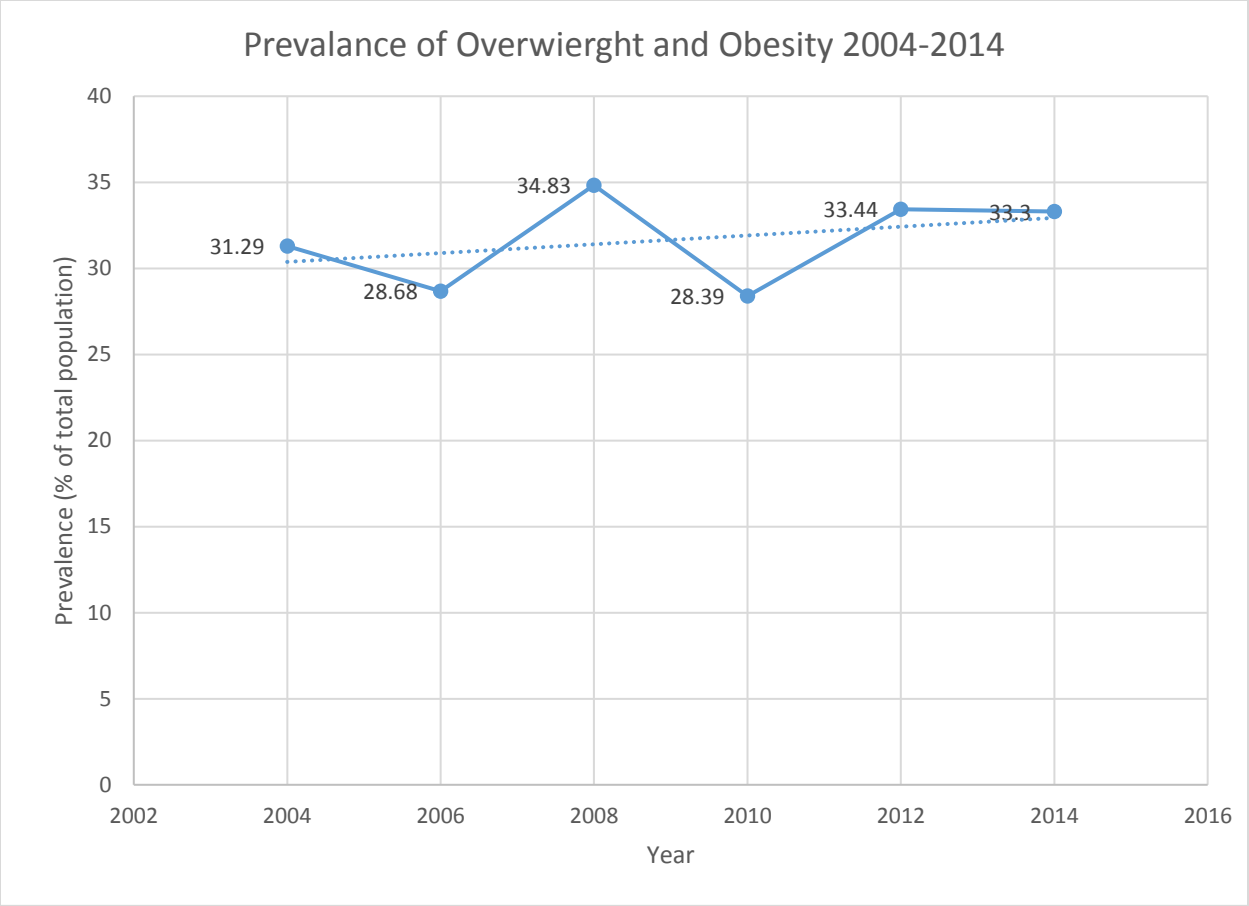

Figure 3: Trend in prevalence of overweightness and obesity during the study period of 2004-2014. Prevalence was derived from the combined weighted frequencies overweigh and obesity for each year. The dashed line represents the linear trend during the time period.

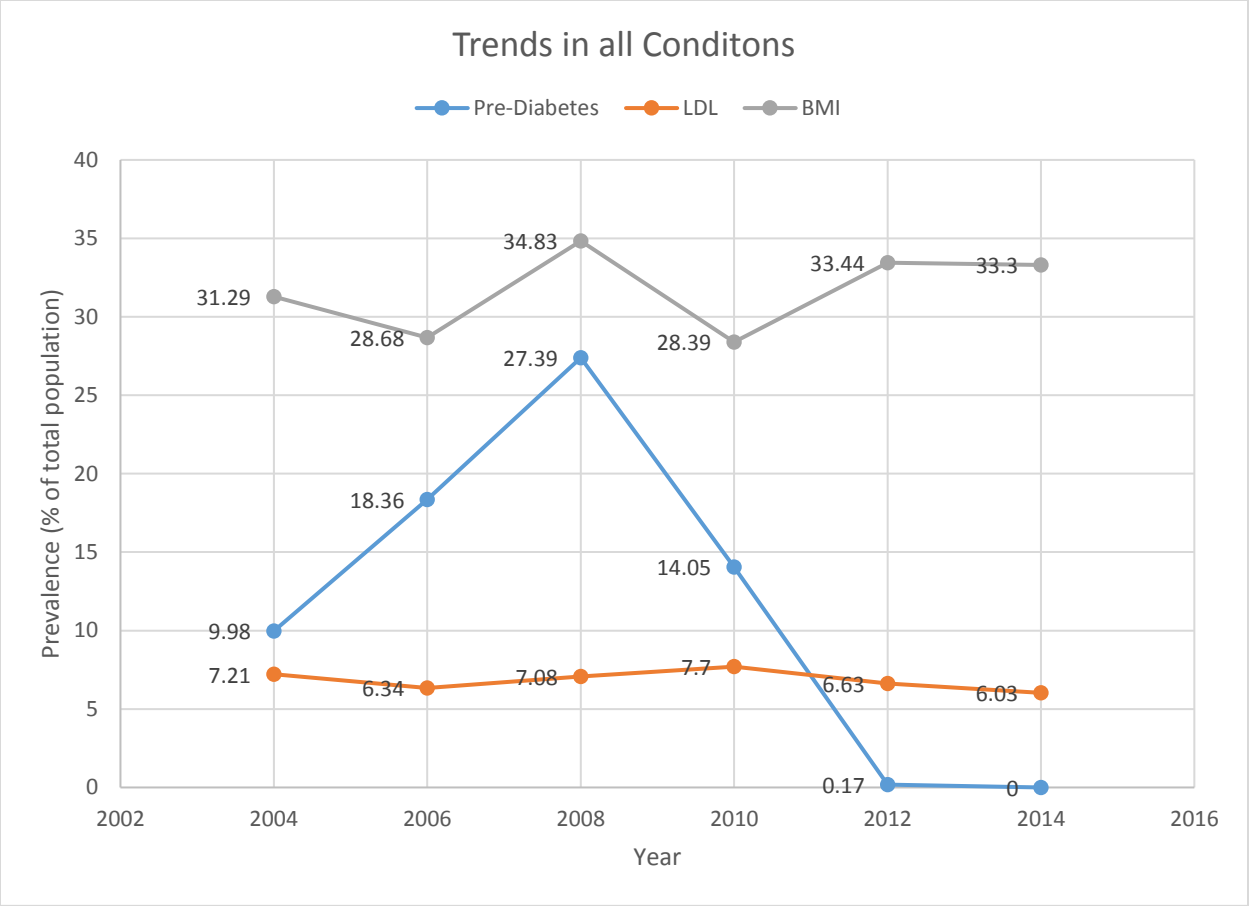

Figure 4: A trend comparison of the previous three figures to see how they vary overtime in relation to each other between 2004-2014. Prevalence was derived from weighted frequencies for each variable for each year.

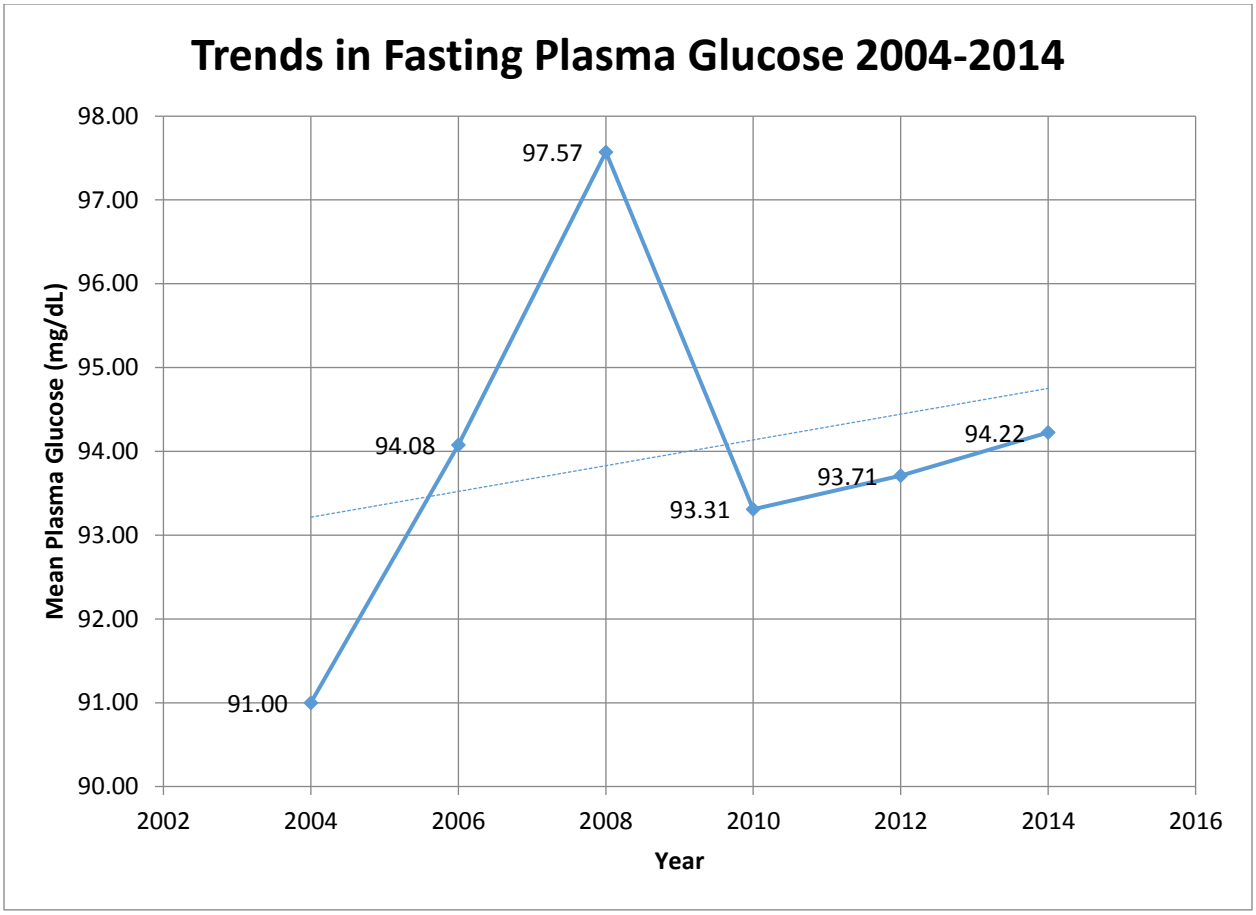

Figure 5: Plasma glucose is biomarker used to determine diabetes status. The graph plots mean plasma glucose during the study period. The dashed line represents the trends over time in mean fasting plasma glucose value.

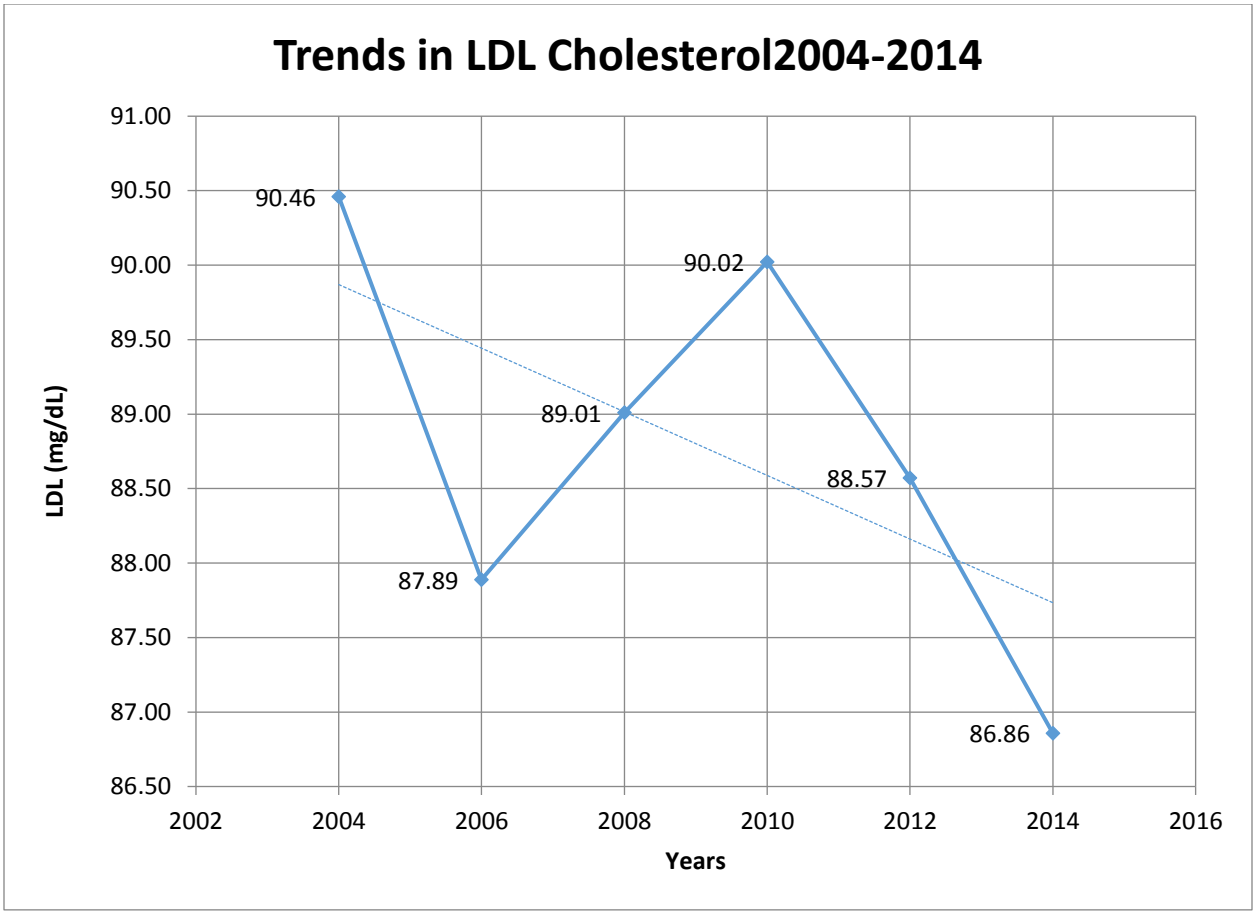

Figure 6: Low density lipoprotein (LDL) is biomarker that was used in this study to define cholesterol status. The graph plots mean LDL value during the study period.. The dashed line represents the trends over time in mean LDL value.

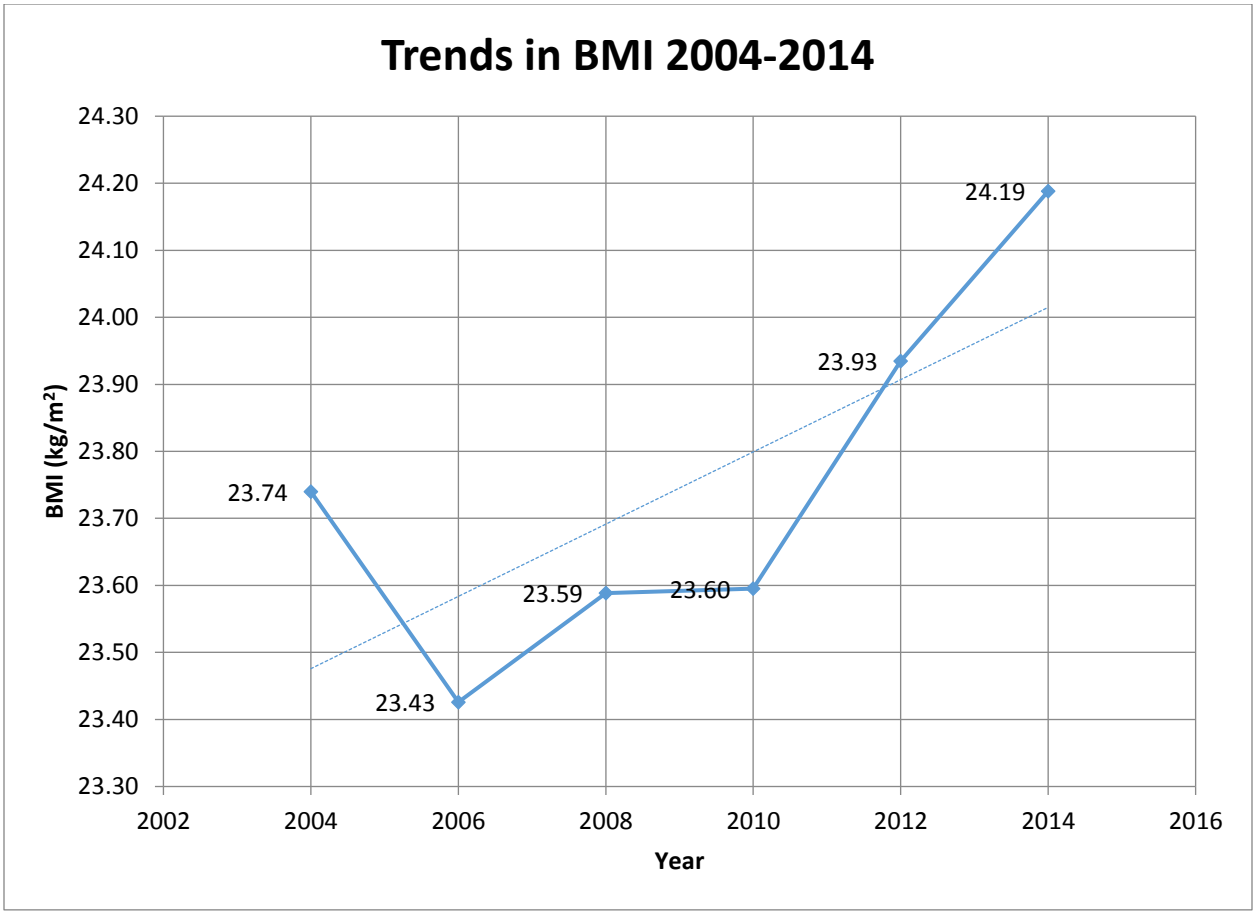

Figure 7: Body Mass Index (BMI) is used in this study to define overweightness and obesity. The graph plots mean BMI during the study period. The dashed line represents the trends over time in mean BMI value.

Year	Diabetes Category	Frequency	Weighted Frequency	Std Err of Wgt Freq
2004	Normal	866	29,631,789	2,522,448
	Pre-Diabetes	82	3,306,623	530,991
	T2DM	4	187,921	118,195
2006	Normal	718	27,227,634	2,302,560
	Pre-Diabetes	164	6,158,284	898,100
	T2DM	6	162,493	107,441
2008	Normal	303	24,132,774	2,543,365
	Pre-Diabetes	133	9,233,848	750,292
	T2DM	5	341,628	162,568
2010	Normal	465	28,453,483	2,250,846
	Pre-Diabetes	96	4,656,405	618,390
	T2DM	1	32,208	32,208
2012	Normal	522	33,653,448	3,040,271

	Pre-Diabetes	2	55,920	42,599
	T2DM	3	89,990	56,383
2014	Normal	534	33,318,750	2,853,252
	Pre-Diabetes	0	0	0
	T2DM	3	215,480	178,321

Table 1: Frequency table illustrating the frequency each diabetes category during each year of the study period. Note that the weight frequencies were used to calculate prevalence values.

Year	BMI Category	Frequency	Weighted Frequency	Std Err of Wgt Freq
2004	Underweight	140	4,947,565	770,868
	Normal	504	5,359,846	805,685
	Overweight	159	17,400,743	1,809,421
	Obese	143	5,239,162	455,178
2006	Underweight	132	5,739,029	716,118
	Normal	456	18,133,325	1,807,773
	Overweight	156	4,963,645	400,476
	Obese	140	4,637,681	870,118
2008	Underweight	66	5,415,630	1,090,447
	Normal	213	16,166,281	1,225,502
	Overweight	100	7,254,304	1,378,743
	Obese	59	4,279,515	1,093,389
2010	Underweight	76	4,431,824	679,585
	Normal	304	19,136,341	1,380,388
	Overweight	97	5,200,511	570,381
	Obese	80	4,143,178	635,772
2012	Underweight	83	4,942,840	618,198
	Normal	268	17,552,044	1,939,878
	Overweight	103	6,465,762	969,480
	Obese	73	4,838,712	785,880
2014	Underweight	80	4,576,979	546,567
	Normal	272	17,791,330	2,324,834
	Overweight	91	5,660,084	932,642
	Obese	94	5,505,838	860,496

Table 2: Frequency table illustrating the frequency each BMI category during each year of the study period. Note that the weight frequencies were used to calculate prevalence values.

Year	Cholesterol Category	Frequency	Weighted Frequency	Std Err of Wgt Freq
2004	Ideal	883	30,755,962	2,375,018
	Borderline	50	1,711,958	396,273
	High	16	512,603	95,741
	Very High	4	164,563	111,420
2006	Ideal	820	31,423,209	2,458,918
	Borderline	59	1,906,167	462,033
	High	8	199,992	88,358
	Very High	1	19,043	19,043
2008	Ideal	412	31,321,697	2,244,972
	Borderline	20	1,793,045	481,412
	High	9	593,509	237,635
	Very High	0	0	0
2010	Ideal	520	30,591,295	2,208,417
	Borderline	32	1,924,780	410,118
	High	7	332,815	140,184
	Very High	3	293,207	185,615
2012	Ideal	489	31,557,413	2,868,239
	Borderline	30	1,841,166	437,043
	High	7	378,133	191,462
	Very High	1	22,645	22,645
2014	Ideal	512	31,511,235	2,588,281
	Borderline	17	1,523,237	521,687
	High	6	443,902	217,638
	Very High	2	55,857	40,112

Table 3: Frequency table illustrating the frequency each cholesterol category during each year of the study period. Note that the weight frequencies were used to calculate prevalence values.

Year	LDL Correlation	P-value	BMI Correlation	P-value2
2004	0.001	0.957	0.110	0.0004
2006	0.027	0.407	0.013	0.6890
2008	0.026	0.571	-0.013	0.7850
2010	0.022	0.600	0.217	<0.0001
2012	0.092	0.032	0.083	0.0520
2014	-0.022	0.598	0.077	0.0630

Table 4: Correlation coefficients for each biomarker with PFG each year, and corresponding p-values.