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Secular and Longitudinal Trends in Body Weight in a Large Population of Veterans, 2000-2014

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ABSTRACT

Secular and Longitudinal Trends in Body Weight in a Large Population of Veterans, 2000-2014

By

Margery Jean Burrage Tamas

December 9, 2015

INTRODUCTION: The prevalence of obesity is increasing in the United States and globally, and impacts many aspects of health. To understand the contribution of body weight to chronic diseases such as diabetes, it is necessary to characterize secular and longitudinal weight trends prior to evaluating the weight effects that may result from medical interventions. The cross-sectional National Health and Nutrition Examination Survey (NHANES) indicates that mean body weight in the adult population increased from 152 lb (69 kg) to 181 lb (82 kg) between 1959 and 2008. However, there are no previously published studies on secular or longitudinal weight trends in a veteran population.

OBJECTIVES: The purpose of this study is to describe secular and longitudinal trends in body weight for a large population of male and female individuals with and without diabetes in the Veterans Administration (VA) healthcare system, the largest integrated healthcare system in the United States.

METHODS: Retrospective observational analysis of data from VA facilities throughout the United States, in patients who had at least 4 outpatient visits within any consecutive 4-year interval during 2000–2014. The dataset included men and women with and without type 2 diabetes. The primary outcomes were longitudinal trends in body weight stratified by birth cohort, sex, and diabetes status.

RESULTS: A total of 4,680,735 unique patients, 1,666,346 with diabetes, were included in the analysis. Regressions were performed on the patient-level data and segmented by birth cohort. A total of 176,034,543 weight observations were included in the analysis, with a median of 15 to 36 weight observations per patient in individuals without diabetes, and a median of 22 to 49 weight observations in individuals with diabetes across birth cohorts. In the year 2000, the y-intercept for the regression equations indicated a mean body weight for men without diabetes of 188 lb (85 kg), for women without diabetes of 166 lb (75 kg), for men with diabetes of 213 lb (97 kg), and for women with diabetes of 195 lb (88 kg). Secular trends in body weight during the study period had median linear increases of 0.53 lb/y (0.24 kg/y) in men with diabetes, 0.50 lb/y (0.23 kg/y) in women with diabetes, 0.53 lb/y (0.24 kg/y) in men without diabetes, and 0.86 lb/y (0.39 kg/y) among women without diabetes, respectively. In cohorts born before 1940, body weight decreased. In the cohorts born between 1940-1949, body weight was stable. In all cohorts born after 1950, body weight increased. Across birth cohorts, the rate of weight increase accelerated from older to younger groups, with higher rates in the groups with diabetes than in the groups without diabetes: $\beta_2 = 0.0260$ lb^2/y (0.01179 kg^2/y) in men without diabetes, 0.0398 lb^2/y

$(0.01805 \text{ kg}^2/\text{y})$ in men with diabetes, $0.0127 \text{ lb}^2/\text{y}$ $(0.00576 \text{ kg}^2/\text{y})$ in women without diabetes, and $0.0895 \text{ lb}^2/\text{y}$ $(0.04060 \text{ kg}^2/\text{y})$ in women with diabetes.

CONCLUSIONS: This is the first report of secular and longitudinal weight trends in a large, contemporary veteran population that includes both men and women. Consistent with findings from the Normative Aging Study, a longitudinal study of male veterans from the northeastern United States, weight changes varied from decreases among the oldest birth cohorts to increases in the youngest birth cohorts. Secular changes in body weight by birth cohort were consistent with the patterns reported in the Global Burden of Disease Study. The rate of weight change is accelerated in all younger birth cohorts relative to all older birth cohorts, with the highest rates in women with diabetes. Further analyses of this dataset are recommended to elucidate clinical characteristics associated with longitudinal weight change among individuals with and without diabetes in the veteran population.

INDEX WORDS: veterans, diabetes, body weight, longitudinal trends, descriptive statistics, epidemiology

SECULAR AND LONGITUDINAL TRENDS IN BODY WEIGHT IN
A LARGE POPULATION OF VETERANS, 2000-2014

by

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A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
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APPROVAL PAGE

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ACKNOWLEDGMENTS

TABLE OF CONTENTS

List of Tables

List of Figures

INTRODUCTION

1.1 Background

1.1.1 Secular and longitudinal trends in body weight

Obesity is a risk factor for many chronic diseases, including diabetes (Ng et al, 2014; Fryar et al, 2014; Samanic et al, 2004). Globally, the prevalence of obesity is increasing (Ng et al, 2014). In the United States, data from the National Health and Nutrition Examination Survey (NHANES) shows that the prevalence of overweight, defined by a body mass index (BMI) of 25 kg/m^2 or more, declined between 1960-2012, but the prevalence of obesity (BMI $\geq$ 30 kg/m^2) and extreme obesity (BMI $\geq$ 40 kg/m^2) has generally increased in both men and women (Fryar et al, 2014).

The Normative Aging Study was a prospective cohort study of 2280 healthy male veterans from the Boston, Massachusetts area recruited in 1961-1970, ranging in age from 30 to 78 years at baseline, and for whom 15-year outcomes for body weight and obesity have been reported (Grinker et al, 1995). The Veterans Administration (VA) healthcare system is the largest integrated healthcare system in the United States, and has a very large electronic medical records database that has been used extensively in epidemiological research in obesity and diabetes (e.g., Gebregziabher et al, 2011; Jackson et al, 2015; Olson et al, 2015; Samanic et al, 2004; Thorpe et al, 2015; Tseng et al, 2014). However, there are no previously published studies on secular or longitudinal weight trends in a large, contemporary veteran population.

1.1.2 Body weight and diabetes

Diabetes is a prevalent chronic disease in the United States, with an estimated population prevalence of 12% to 14% (Menke et al, 2015). Type 2 diabetes is vastly more prevalent than type 1 diabetes: the best estimate of type 1 prevalence in the noninstitutionalized civilian population is 0.26% to 0.34% (Menke et al, 2013). Diabetes has a prevalence of approximately 25% within the VA healthcare system (US Department of Veterans Affairs, 2015).

Among patients with diabetes, interventions to improve glycemic control are often measured by their effects on glycated hemoglobin (A1C) (Inzucchi et al, 2015). However, A1C reduction is generally associated with weight gain (Horton et al, 2010; Fonseca et al, 2013; Abraira et al, 2009). Hence, the effects of interventions for diabetes need to be separated from secular trends toward weight increase that have been observed in individuals with and without diabetes (Ng et al, 2014; Morgan et al, 2012; Krieger et al, 2013; Fryar et al, 2014).

Insulin is always used to treat type 1 diabetes, but many different classes of medications are used to treat type 2 diabetes (Menke et al, 2013; Inzucchi et al, 2015). Type 2 diabetes mellitus is characterized by chronic hyperglycemia due to insulin resistance coupled with progressive pancreatic beta-cell failure (Kahn, 2003). Because of the progression of beta-cell loss, exogenous insulin therapy eventually becomes necessary for many patients with type 2 diabetes (Khunti et al, 2015; Inzucchi et al, 2015; Zinman, 1989).

Current treatment algorithms for the management of type 2 diabetes from the American Diabetes Association (ADA) (Inzucchi et al, 2015) recommend insulin throughout the progression of the disease. The ADA recommends initiating treatment with metformin, an oral agent, unless A1C is severely elevated (A1C $\geq$ 9%), in which case insulin is the preferred agent (Inzucchi et al, 2015). In type 2 diabetes, insulin is also recommended for use in combination with other antihyperglycemic agents (Inzucchi et al, 2015).

Insulin use is generally associated with weight gain, and is considered more likely than other antihyperglycemic medications to be associated with weight gain > 5% (Horton et al, 2010; Morgan et al, 2012). As insulin is the most efficacious agent for reducing A1C (Inzucchi et al, 2015), there is a need to differentiate an insulin-specific effect on body weight from effects associated with reducing A1C (Huizinga et al, 2008). Other investigators have noted that weight gain of approximately 2 kg for every 1% reduction in A1C follows the initiation of insulin or sulfonylureas (UKPDS 28, UKPDS 33). Avoiding weight gain with intensification of glycemic control is of great practical interest to clinicians and to individuals with type 2 diabetes.

Other factors that may affect body weight in individuals with diabetes are the effects of certain other medications for comorbid conditions (Kushner & Ryan, 2014), hypoglycemia (Sanders et al, 2006; Seaquist et al, 2013), smoking (Fonseca et al, 2013; Grinker et al, 1995), and lifestyle interventions (Look AHEAD Study Group, 2014; Jackson et al, 2015).

1.2 Aims

This thesis represents the first portion of a larger study that is intended to assess changes in body weight as a function of changes in glycemic control with insulin therapy, accounting for the effects of hypoglycemia, other medications known to affect body weight, smoking, and lifestyle interventions, all while controlling for secular trends in body weight. A retrospective study of 6032 individuals in general practice in the United Kingdom found that 1 year after initiating insulin therapy, body weight increased by 2.2 kg and A1C decreased by 1.4%, but the overall range of weight change was –60 kg to 60 kg, and the range of A1C change was –15% to 15% (Owen et al, 2010). Other than noting that patients using premixed insulin therapy exhibited the greatest weight gain, the authors offer no explanation for the extreme weight changes.

Of the 4 aims of the larger proposed study, this thesis mainly addresses Aim 1.

1.2.1 Aim 1

To compare longitudinal trends in body weight among individuals with and without type 2 diabetes.

1.2.2 Aim 2

To determine the relationship between changes in body weight and changes in A1C among individuals with type 2 diabetes, according to whether they initiated insulin or some other antihyperglycemic medication.

1.2.3 Aim 3

To determine whether participation in the MOVE! lifestyle intervention alters the relationship between change in body weight and change in A1C among the individuals with type 2 diabetes.

1.2.4 Aim 4

To determine whether hypoglycemia alters the relationship between change in body weight and change in A1C among the individuals with type 2 diabetes.

1.3 Hypotheses

The hypotheses listed below represent all of the hypotheses for the larger, overall study. Data presented in this thesis are limited to longitudinal and secular weight trends in men and women with and without diabetes for hypothesis 1, and A1C distribution and smoking status for hypothesis 2.

1.3.1 Hypothesis 1

Body weight will increase with time in all groups (e.g., individuals with and without diabetes, men and women).

1.3.2 Hypothesis 2

For a given change in A1C, patients initiating insulin therapy will have a greater change in body weight than patients who initiate one of the noninsulin therapies (i.e., the change in body weight per 1-unit change in A1C will differ depending on whether insulin or a noninsulin treatment is initiated).

1.3.3 Hypothesis 3

Participants in the VA lifestyle intervention MOVE! will have less weight gain per unit change in A1C than nonparticipants.

1.3.4 Hypothesis 4

Individuals with hypoglycemia will gain more weight than individuals without hypoglycemia.

REVIEW OF THE LITERATURE

2.1 Population Trends in Body Weight

In terms of the first goal of the larger study (Aim 1), it is important to elucidate secular and longitudinal trends in weight change according to sex and birth cohort.

2.1.1 Global trends and trends outside the United States

The Global Burden of Disease Study found that in developed countries, the prevalence of obesity increases with age, and that the rate of increase is higher in younger birth cohorts than in older cohorts (Ng et al, 2014). Both the prevalence and the rate of development of obesity with age are higher in women (Ng et al, 2014). Morgan et al (2012), studying the UK general practice population, found that body weight increased from 1995-2010 in adult men and women with or without diabetes.

2.1.2 Trends in the United States

Ogden et al (2015) estimated the crude prevalence of obesity among adults in the United States during 2011-2014 at 36.5%. Prevalence was higher among women (38.3%) than among men (34.3%) (Ogden et al, 2015). Similar patterns of obesity by age were seen in both men and women, with the highest rates among individuals aged 40-59 years, the second-highest rates among individuals aged 60 years and over, and the lowest rates among individuals aged 20-39 years (Ogden et al, 2015). In terms of race and ethnicity, among adults, non-Hispanic blacks had the highest rate of obesity (48.1%), followed by Hispanic individuals (42.5%), non-Hispanic whites (34.5%), and non-Hispanic Asians (11.7%) (Ogden et al, 2015). Analyses of data collected

from the NHANES shows that the mean body weight of the population in the United States increased from 1959-2008 (Krieger et al, 2013).

Individuals with diabetes are even more likely to be overweight or obese than individuals who do not have diabetes (CDC, 2004). In NHANES 1999-2002, 30.5% of the population aged $\geq$ 20 years was overweight or obese, but 85.2% of adults with diagnosed diabetes were overweight or obese, although women with diabetes were somewhat less likely than men with diabetes to be overweight or obese (84.2% vs 86.3%, respectively) (CDC, 2004). Mexican individuals with diabetes had the highest prevalence of obesity (86.9%), followed by non-Hispanic blacks with diabetes (86.1%), and non-Hispanic whites with diabetes (85.9%) (CDC, 2004). The prevalence of obesity and overweight was higher overall and in every subgroup in 1999-2002 than in NHANES III (1988-1994) (CDC, 2004).

2.1.3 Trends in veteran populations

In the Normative Aging Study previously described, among the 867 men with data available for 15 years, the authors state that major secular differences were observed, with the younger cohorts exhibiting higher body weight at the same ages as men from the older cohorts (Grinker et al, 1995). The mean $\pm$ SD change in body weight over 15 years among participants aged 30-34 years at baseline was 2.65 $\pm$ 6.54 kg, whereas the participants aged $\geq$ 60 years lost weight (-4.11 ± 4.99 kg) (Grinker et al, 1995). The coefficient of the first-order linear regression equation was -0.469 kg/y, *P* < .001 for trend (Grinker et al, 1995). Similar patterns of results were found for trends in BMI with birth cohort and with time: BMI increased by 1.03 $\pm$ 2.13 kg/m^2 in the participants aged 30-34 years at baseline, but the change was -0.69 ± 1.78 kg/m^2 in the participants aged $\geq$ 60 years at baseline, *P* < .001 for trend (Grinker et al, 1995).

Smoking cessation was identified as an important contributor to weight gain (Grinker et al, 1995). A 3-way classification scheme was used to identify smoking status: never smoked or quit before the study (65%), always smoked (16%), or quit during the study (18%) (Grinker et al, 1995). Individuals who quit during the study had the greatest BMI increase, approximately 1.55 kg/m^2, while those who always smoked had the least BMI increase, approximately 0.4 kg/m^2, and the third group had an intermediate BMI increase of approximately 0.7 kg/m^2 (Grinker et al, 1995).

Accordingly, the current study describes trends in body weight in men and women with and without diabetes.

2.2 Weight Change and Insulin Initiation

In terms of the goals of the larger study (Aims 2-4), it is important to distinguish treatment-associated weight gain, as may occur with insulin therapy, from secular trends in weight change according to sex and birth cohort.

2.2.1 Weight Change and Insulin Initiation--Randomized Controlled Trials With Weight Change as a Primary Endpoint

After searching PubMed and the references cited in the meta-analyses by Pontiroli (2011 and 2012), only 4 small RCTs (Barratt et al [2008], Jacob et al [2007], Yki-Jarvinen et al [1999], and Makimattila et al [1999]) were identified which investigated insulin initiation in T2DM with weight change as a primary endpoint. Makimattila et al (1999) published a small RCT (N = 26) which included a graph of weight change versus change in fasting glucose over 1 year. Mean weight gains of 3.8 kg and 7.5 kg were reported in the 2 arms of the trial, but 2 outlier weight gains (17 kg and 22 kg) were not discussed.

2.2.2 Weight Change and Insulin Initiation--Other Randomized Controlled Trials

Weight change is commonly measured in clinical trials of insulin therapy, and the reported range of weight gain is large.

A meta-analysis of weight change data from 143 insulin arms of 67 randomized controlled trials of 12-52 weeks duration (Pontiroli et al [2011] and Pontiroli et al [2012]) found that insulin initiation was associated with an annualized weight gain of 4.3 ± 2.74 kg (mean $\pm$ sd; range: -2.76 to 14.7 kg). Of the study arms included in these papers, only 4 demonstrated a mean weight loss.

The largest (N = 12,443) and longest RCT of insulin therapy, the ORIGIN trial (2012), found that insulin treatment resulted in a median weight gain of 1.6 kg over 6.2 years compared with 0.5 kg median weight loss in the standard care group.

2.2.3 Weight Change and Insulin Initiation--Observational Studies

Few studies report the range or distribution of change in body weight after insulin initiation. A study of the UK Health Improvement Network database by Owen et al (2010) found that weight increased 2.2 kg ($P < .001$) and A1C was reduced by 1.4% ($P < .001$) in the first year after insulin initiation. However, a scatter plot included in this publication indicated that many of the 6032 patients analyzed gained or lost more than 20 kg within the first year of insulin initiation (Owen et al, 2010). The authors noted that patients using premixed insulins were more likely to gain weight than patients using other types of insulin regimens, but offered no further comment on the extreme range of weight change observed in routine clinical general practice (range: ≈ -60 kg to ≈ 60 kg).

Feldstein et al (2008) studied a population of patients in the Kaiser Permanente health system and distinguished 4 different weight trajectories in the first year following the diagnosis of type 2 diabetes: high stable weight, lower stable weight, weight gain, and weight loss. For this

population, 18.3% followed the high stable weight trajectory, 54.1% followed the lower stable weight trajectory, 16.0% followed the weight gain trajectory, and 11.6% followed the weight loss trajectory (Feldstein et al, 2008). About 75% of the individuals following the weight loss trajectory had A1C < 7% at 1 year, whereas only 44.3% of the individuals following the weight gain trajectory had A1C < 7% at 1 year (Feldstein et al, 2008). Contrasting results were also seen among individuals with A1C ≥ 9% at 1 year, comprising 2.7% of those on the weight loss trajectory, and 16% of those on the weight gain trajectory (Feldstein et al, 2008).

The 12-nation, observational CREDIT study reported that 1 year after insulin initiation in 2179 patients with type 2 diabetes, the mean weight gain was 1.78 kg (median 2.0 kg), and 24% of participants gained ≥ 5 kg (Balkau et al, 2015). The distribution of weight gain and loss was symmetrically distributed around the mean, with a range of weight change varying from −20 kg to 22 kg (Balkau et al, 2015). CREDIT found notable country-by-country variation in the mean weight gain, from as little as 0.95 kg in Germany to as much as 4.26 kg in Portugal (Balkau et al, 2015). After adjusting for recruitment center, only a higher baseline A1C, a lower baseline BMI, and a higher insulin dose at baseline and at 1 year predicted weight gain; no relationship between weight change and change in A1C was found on multivariate analysis (Balkau et al, 2015). CREDIT did not include a control group.

A similar range of weight change was found by van Dieren et al (2012) in a post hoc analysis of ADVANCE (N = 11,140). This RCT was not an insulin therapy trial per se, but a trial of intensive versus standard glycemic control, suggesting that extreme weight change may be more a function of glycemic control rather than insulin therapy specifically. Both Balkau and van Dieren published histograms of individual-level weight changes, and in both papers, the distribution of weight change appears symmetrical around the mean.

A small (N = 122) prospective observational study by Jansen et al (2011) prospectively followed patients initiating insulin therapy for 3 years and found that only 12% of the weight gain in the first 9 months after insulin initiation was explained by changes in glycemic control. A prospective 1-year study of 74 patients by Jansen et al (2014) found that weight change ranged from –6 kg to 19 kg, with 71% of patients gaining weight and 29% maintaining or losing weight. The authors recommended initiating insulin at a low dose and gradually uptitrating to avoid weight gain.

2.3 Weight Change and Intensive Diabetes Management

Several large randomized trials of intensive diabetes therapy individuals with type 2 diabetes have generated longitudinal data on body weight by treatment group, e.g., VADT, ACCORD, and ADVANCE (Abraira et al, 2009; Fonseca et al, 2013; van Dieren et al, 2012). In the VADT (Abraira et al, 2009) and the ACCORD (Fonseca et al, 2013) studies, higher weight gain was observed in the intensive treatment arms. By contrast, body weight remained stable in the intensive treatment arm of ADVANCE (van Dieren et al, 2012). The ADVANCE trial demonstrated a symmetric distribution of weight gain and loss about the mean with intensive or standard glycemic control, with the distribution skewed toward greater weight gain in the intensive control group (van Dieren et al, 2012).

2.4 Weight Change and Hypoglycemia

There are at least two mechanisms by which hypoglycemia might cause weight gain, and both have been demonstrated in animal models: hypoglycemia-induced overfeeding (e.g., Sanders et al [2006]) and reduced physical activity following repeated episodes of severe hypoglycemia (McNay et al, 2013). Hypoglycemia as a factor that might modify the relationship between

changes in glycemia and weight with insulin therapy in humans with type 2 diabetes has not

previously been studied, although a meta-analysis by Pontiroli et al (2011) showed that mean

weight gain was positively correlated with the proportion of individuals reporting hypoglycemia.

Cardiovascular risk factors are more prevalent in the VA population both before and after

diagnosis of diabetes (Olson et al, 2015). Current treatment guidelines for hypertension in type 2

diabetes recommend angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor

blockers (ARBs) as first-line therapy (Fox et al, 2015). Interestingly, a common genetic

polymorphism (rs1799752) increases the risk of severe hypoglycemia with ACE inhibitor usage

(Gard, 2010). The deletion (D) allele of the ACE gene is estimated to occur in about 55% of the

population (Gard, 2010). In the Fremantle Diabetes Study, individuals with the DD genotype

were at 2-fold higher risk of severe hypoglycemia (Davis et al, 2011). Although ACE genotype

does not appear to affect blood pressure response to ACE inhibitors, these agents may precipitate

hypoglycemia in patients with diabetes (Jarred & Kennedy, 2010; Morris et al, 1997).

Antihypertensive medications are widely used in the VA population (Olson et al, 2015; Jackson et

al, 2015; Thorpe et al, 2015).

Within the VA Healthcare System, older patients with multiple comorbidities are often

maintained at levels of glycemic control which increase the risk of hypoglycemia (Tseng et al,

2014). Comorbid dementia further increases the risk of hypoglycemia in older veterans with type

2 diabetes (Thorpe et al, 2015).

2.5 Weight Change and Other Medications

Many types of drugs, including many antihyperglycemic agents, affect body weight

(Kushner & Ryan, 2014). Antihyperglycemic agents associated with weight gain include insulin,

sulfonylureas, and thiazolidinediones (Kushner & Ryan, 2014; Inzucchi et al, 2015). Dipeptidyl

peptidase-4 (DPP-4) inhibitors are considered weight-neutral; metformin is considered weight-neutral to weight sparing, and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium glucose cotransporter-2 (SGLT2) inhibitors are considered to promote weight loss (Inzucchi et al, 2015). Current treatment guidelines for type 2 diabetes include explicit consideration of their effects on body weight, but do not consider the effects of concomitant medications that may be prescribed for common comorbidities of diabetes, such as depression (Dumbreck et al, 2015).

Individuals with type 2 diabetes are more likely to have depression than individuals who do not have type 2 diabetes (Mezuk et al, 2015), and are therefore at higher risk of exposure to antidepressant drugs. Some antidepressants (e.g., amitriptyline, imipramine, nortriptyline, paroxetine), some anticonvulsants (e.g., valproate), and steroid hormones (e.g., glucocorticoids) are associated with weight gain (Kushner & Ryan, 2014). By contrast, other antidepressants (e.g., fluoxetine, sertraline, bupropion), and other anticonvulsants (e.g., topiramate, lamotrigine) are associated with weight loss (Kushner & Ryan, 2014). A recent study of the US Medicare population found that 2.5% of individuals with comorbid type 2 diabetes and depression were prescribed tricyclic antidepressants (Lorgunpai et al, 2014), potentially increasing their risk of weight gain.

Within the VA system, off-label use of antipsychotic medication is common among patients with posttraumatic stress disorder, minor depression, major depression, anxiety, and dementia; these drugs are also used for their on-label indications of schizophrenia or bipolar disorder (Leslie et al, 2009). Several neuroleptic agents (e.g., haloperidol, olanzapine, quetiapine, risperidone) are associated with pronounced weight gain (Kushner & Ryan, 2014). The concomitant use of rosiglitazone, a thiazolidinedione used to improve insulin sensitivity and

reduce blood glucose levels, and olanzapine, an antipsychotic agent, was associated with a weight gain of 3.2 ± 4.5 kg over 12 weeks in a small randomized controlled trial of individuals with schizophrenia (Baptista et al, 2009).

Thus, any study of longitudinal weight outcomes in patients with type 2 diabetes needs to consider the possibility that the results will be confounded by concomitant medications.

2.6 Weight Change and Smoking Status

Van Dieren et al (2012) identified smoking status as one of the primary patient characteristics predicting weight gain with insulin initiation in the ADVANCE trial; the other factors were age, ethnicity, and baseline A1C. The use of insulin in combination with thiazolidinediones was the most important treatment-related predictor (van Dieren et al, 2012). Similarly, in the ACCORD trial, Fonseca et al (2013) found that smoking status was strongly associated with weight gain, with the highest gains among current smokers.

Feldstein et al (2008) found that quitting smoking was one of the factors significantly associated with weight gain in the first year after diagnosis of type 2 diabetes; the other factors associated with weight gain were sulfonylurea use or not seeing a nutritionist. Insulin use was more common among those who gained weight (2.3%) than those who lost weight (1.1%), but not significantly so ($P = .062$) (Feldstein et al, 2008).

Smoking cessation was also identified as an important contributor to weight gain in the Normative Aging Study (Grinker et al, 1995). A 3-way classification scheme was used to identify smoking status: never smoked or quit before the study (65%), always smoked (16%), or quit during the study (18%) (Grinker et al, 1995). Individuals who quit during the study had the greatest BMI increase, approximately 1.55 kg/m^2, while those who always smoked had the least

BMI increase, approximately 0.4 kg/m^2, and the third group had an intermediate BMI increase of approximately 0.7 kg/m^2 (Grinker et al, 1995).

2.7 Efficacy of Lifestyle Interventions to Mitigate Weight Gain With Interventions for Diabetes

In people with type 2 diabetes, a number of behavioral and psychosocial factors may contribute to overeating, and consequent weight gain, including depression and fatalism (e.g., TODAY Study Group, 2011; Walker et al, 2012). Limited data are available on which to base recommendations for lifestyle interventions to mitigate weight gain in patients with diabetes, whether or not they are treated with insulin therapy (Look AHEAD Research Group, 2014; Jackson et al, 2015; Russell-Jones & Khan, 2007). Increasing physical activity and reducing caloric intake are often recommended to patients with type 2 diabetes to mitigate weight gain, but it is unclear whether general recommendations concerning the type of activity and intensity needed to maintain or lose weight also apply when insulin is initiated.

Barratt (N = 50) compared an intensive self-management education intervention with standard education, and found that over 6 months, participants in the standard group gained a mean 4.6 kg but that participants in the intensive group lost a mean 0.6 kg.

The Look AHEAD study demonstrated that both intensive lifestyle intervention and diabetes self-management resulted in beneficial weight loss in a population with diabetes (Look AHEAD Research Group, 2014). With regard to the VA population, previous research has shown that participation in the MOVE! lifestyle change program was associated with weight loss, but its efficacy in the subgroup of participants with diabetes at baseline (23% of the study population) have not been reported separately from the overall results (Jackson et al, 2015). It would be of interest to know whether the VA's MOVE! lifestyle change program, already implemented

throughout the VA system, mitigates weight gain following insulin initiation (Jackson et al, 2015).

METHODS AND PROCEDURES

3.1 Context of Study

The Department of Veteran Affairs Clinical Data Warehouses (CDW) databases were interrogated and selected data analyzed on the VA Informatics and Computing Infrastructure (VINCI) platform. These data were used to assess secular and longitudinal trends in body weight in men and women with and without diabetes. In the future, these data will be used to compare the change in body weight and change in A1C after the initiation of insulin and other antihyperglycemic medications in type 2 diabetes, then determine whether this relationship is altered by participation in the MOVE! lifestyle intervention or by hypoglycemia, smoking status, or other medications that may affect body weight. The data were obtained from the Institutional Review Board-approved data repository, "VA Diabetes Related Epidemiological Analyses" eIRB #66117.

No prior studies of longitudinal and secular weight trends in a large, contemporary VA population have been published.

3.2 Data Selection for Hypothesis 1

In the VA CDW, demographic data, health factor data (e.g., smoking status), primary care study visit data, medication data, and laboratory measurements are all stored separately and indexed by various patient identification numbers, including a nationally unique patient identification code number, identified in this study as PatientICN. Datasets for analysis are assembled from CDW components through SQL queries and various sorting and merging operations in SAS, as indicated in Figure 3.1a. The CDW files were searched for patients with or

without diabetes who had at least one measurement of body weight (and BMI) during primary care visits within each of 4 consecutive calendar years during 2000-2014, hereafter referred to as "the study period." For each patient included in the dataset, demographic information such as age, sex, race, ethnicity, and income was requested, as well as clinical data such as body weight and smoking status.

Weight observations are customarily recorded in English units of measurement in the VA healthcare system. Weight observations were selected according to a 2-step process. In the first step, weight observations outside the range 0-1000 lb were excluded to eliminate invalid data. Weight observations at the extremes of the measurement range may result from disease processes atypical of those seen in the majority of patients with obesity and/or diabetes. Analyses based on extreme outliers may not be generalizable to other outpatient populations with obesity and/or diabetes. Accordingly, in a second step, individual weight observations were excluded if they were below 80 lb (36.4 kg) or greater than 600 lb (272.7 kg); 0.09% of observations were less than 80 lb, and fewer than 0.01% were more than 600 lb.

Concordant with the methods used in other Atlanta VA research (e.g., Olson et al, 2015; Jackson et al, 2015), patients were classified as having diabetes if they had at least one use of ICD-9 code of 250.xx in conjunction with an outpatient visit with a primary care attending, if they had any two uses of the 250.xx ICD-9 codes, or if they had been prescribed an antihyperglycemic medication at any time during the study period. The peak incidence of type 1 diabetes occurs between 5-14 years of age, so individuals diagnosed with diabetes between the ages of 25-85 years are more likely to have type 2 diabetes than type 1 diabetes (Lawrence et al, 2014).

Patients with diabetes who had at least 4 measurements of A1C and body weight were identified. At least 1 A1C measurement in each of 4 consecutive calendar years was required for patients with diabetes to be included in the dataset.

Individuals with at least 4 weight measurements but who did not satisfy the criteria for diabetes were considered to be without diabetes. No inclusion criteria pertaining to A1C measurements were applied to these individuals.

Race was classified using substring searches on the raw race variable. Any use of "white" was classified as white, any use of "black" was classified as black, any use of "asia" was classified as other, any use of "native" was classified as other, any use of "unknown" was classified as unknown.

Primary analyses were performed on all available weight observations of the patients who were aged 25-85 years at any time during the study period. Birth years outside the range 1915-1984 were excluded. A total of 176,034,543 weight observations were included in the primary analysis.

3.3 Data Selection for Hypotheses 2-4

Although this thesis deals primarily with Hypothesis 1, some progress was made in terms of data selection needed to address Hypotheses 2-4. Data for A1C and smoking status have already been pulled and partly analyzed. No other data have been pulled or prepared for analysis. Data selection procedures for hypotheses 2-4 are summarized in Figure 3.1b.

3.3.1 Data selection completed

A1C observations were obtained from the CDW laboratory measurements file. All A1C observations for the unique patients with diabetes who met the criteria for primary care visits and weight observations from 2000-2014 were obtained. A1C observations are customarily recorded

in percent in the VA healthcare system. A1C observations outside the range 0%-100% are meaningless, while those at the extremes of the measurement range may result from disease processes atypical of those seen in the majority of patients with diabetes. A 2-step procedure was used to select A1C values. In the first step, A1C values outside the range 0%-100% were excluded. Analyses based on extreme outliers may not be generalizable to other outpatient populations with diabetes. Accordingly, in a second step, A1C observations were excluded if they were below 4% or above 20%; 0.03% of observations were less than 4%, fewer than 0.001% were more than 20%. This yielded 30,769,962 A1C observations for analysis.

Smoking status was obtained from the CDW health factors file. Smoking status observations were obtained from 4,723,383 unique individuals with and without diabetes who met the criteria for primary care visits and weight observations from 2000-2014. Patients were classified by the most recently reported smoking status unless it was contradicted by previous status reports. Smoking status was considered current if they reported current in the most recent visit. For all other statuses, the previous statuses were reviewed, and patients were classified according to a hierarchy, in which former smokers included anyone who previously reported current or former tobacco use, and nonsmokers included only individuals who consistently reported tobacco nonuse. All other patterns of responses were classified as unknown, or missing, if null.

3.3.2 Data selection methods recommended for future analyses

Medication data is stored in a separate file in the CDW and will be obtained for each unique individual in the dataset. Antihyperglycemic medication use will be assessed for each unique agent in classes HS501 and HS502. Initiation of an antihyperglycemic drug will be considered to have occurred if no prescriptions of the drug of interest occur in the first 2

consecutive calendar years, but occur in both the third and fourth calendar year. Elements of this study plan are similar to those described in other research published by investigators at the Atlanta VA Medical Center, e.g., Olson et al (2015). It may also be desirable to classify agents using the scheme suggested by Thorpe et al (2015), which was also performed in a VA population (insulin only, insulin + other agents, noninsulin agents, no agents). In addition to antihyperglycemic medications, other medications associated with a risk of weight loss or weight gain will be assessed, possibly using the same methodology as Jackson et al (2015). Alternatively, a detailed list of medications associated with weight gain and weight loss could be compiled from the literature and prescribing information.

Data files for the MOVE! participants are recorded in a file at the Atlanta VA Medical Center. Participation in MOVE! will be coded in categories (e.g., none, any, intense-and-sustained) as per Jackson et al (2015).

Diagnostic codes will be used to identify patients with hypoglycemia. Hypoglycemia will be defined as any use of the 251.x ICD-9 codes (Seaquist et al, 2013). While many patients with type 2 diabetes have episodes of hypoglycemia where the 251.x code is not used, the total number of 251.x codes will be counted to approximate the number of hypoglycemic episodes which reached a clinical threshold of concern as shown by the use of the code.

Descriptive statistics (including density plots of weight change vs A1C change by antihyperglycemic medication in groups with type 2 diabetes), and the distribution of weight change for each type of antihyperglycemic medication, will be obtained.

Changes in body weight over time in the insulin groups, noninsulin groups, and nondiabetic controls will be assessed with using generalized estimating equations (GEE) or generalized linear mixed modeling (GLMM), as desirable or necessary, so that any cluster effects

by facility can be properly ascertained, and repeated measures accounted for. The final selection of analytical procedures will be made in consultation with a statistician.

The relationships between change in A1C and change in body weight according to MOVE! participation status, hypoglycemia status, age, sex, race/ethnicity, facility, smoking status, and use of other medications that may influence weight as additional factors modifying the relationship between change in A1C and change in body weight will be assessed with a suitable statistical technique.

3.4 Statistical Analysis

3.4.1 Statistical Analysis for Hypothesis 1

Frequency counts and distributions of the number of unique patients by diabetes status, sex, race, and birth cohort were obtained using PROC FREQ. Mean, standard deviation, median, interquartile range, minimum, and maximum values of age were calculated using PROC MEANS.

Frequency counts of the weight observations and distributions by diabetes status, sex, race, and birth cohort were obtained using PROC FREQ. Mean, standard deviation, median, interquartile range, minimum, and maximum values of body weight by study year were calculated using PROC MEANS, and selected results graphed in SAS or Excel. From these data, secular trends in body weight were obtained in Excel. Linear regression and correlation were performed in Excel and the results graphed.

Longitudinal changes in mean body weight for all of the patients were plotted. To ascertain general trends in the data, PROC SGPLOT with penalized b-splines (PBSPLINE option) for mean body weight by birth year across individuals were calculated from all available weight

observations. These data were stratified by birth cohort, sex, and diabetes status. Each birth cohort consisted of a nonoverlapping 5-year interval between 1915-1984.

Most statistical calculations and selected graphs were performed using SAS version 9.4 (Cary, NC, USA). Other selected graphs, linear regression, and correlation were performed using Excel (Microsoft, Redmond, WA, USA). Chi square analyses and unpaired t-tests of the baseline data were performed using an online calculator (http://www.quantpsy.org/chisq/chisq.htm and http://www.graphpad.com/quickcalcs/ttest1.cfm?Format=SD). Conversion of correlation coefficients to *P*-values was performed with an online calculator (http://www.danielsoper.com/ statcalc3/calc.aspx?id=44). Statistical tests were two-sided and performed at a 5% level of significance.

Of note, none of the analyses performed for this thesis used techniques such as generalized estimating equations (GEE) or other methods that account for the autocorrelation that occurs with repeated measures, since all such methods are unavailable in the VA's current implementation of SAS 9.4.

All statistical analyses for weight were performed in pounds. Results have been reported in pounds and in kilograms. A conversion factor of 2.2046 lb/kg was used and results rounded to 2-4 decimal places for weight measurements and regression coefficients.

3.4.2 Statistical Analyses of Hypotheses 2-4

Descriptive statistics for the A1C data were obtained, including the mean, standard deviation, median, interquartile range, and distribution of A1C values using PROC MEANS and the histogram option in PROC SGPLOT.

Frequency counts of smoking status were obtained and a pie chart was graphed in Excel.

There are two statistical techniques that may be helpful in determining the extent to which body weight is influenced by changes in A1C. The first is generalized estimating equations (GEE). GEE can handle continuous, discrete, and count variables all in the same model, and handles repeated measures. GEE is available in SAS through PROC GENMOD. Alternatively, generalized linear mixed models (GLMM) could be used if it is necessary to allow a subset of the regression coefficients to vary randomly from one individual to another. In SAS, GLMM can be invoked through PROC GLIMMIX.

RESULTS

4.1 Descriptive Statistics

Demographic characteristics of the study population are shown in Table 4.1. A total of 4.68 million patients are included in the dataset, and 35.6% have diabetes. Consistent with the VA population, males (92.06%) and whites (78.49%) constitute the majority of patients. Individuals with diabetes are significantly older than individuals without diabetes ($P < .0001$). In terms of race categories, whites are the oldest and blacks are the youngest groups. The distribution of unique patients by race, sex, and diabetes status is shown in Figure 4.1. The number of individuals within each of the 16 subgroups ranges from 79,517 for females of unknown race with diabetes to 2.235 million for males of white race without diabetes. The distribution of unique patients by birth year is shown in Figure 4.2. The birth years appear to follow a bimodal distribution, with a primary peak at 1947, and a secondary peak at 1932.

A total of 12 consecutive overlapping 4-year time periods are included within the 15-year study window (e.g., 2000-2003, 2001-2004, 2002-2005, … 2011-2014). The mean number of data intervals per veteran was 5.76 ± 3.59 intervals, corresponding to an average of about 8 years of longitudinal data per veteran.

The proportion of the study population with and without diabetes, by birth cohort and sex, is shown in Table 4.2. The proportion with diabetes ranges from 5% to 40%, with peak prevalence in the 1940-1944 cohort.

The distribution of weight observations by frequency are shown in Figure 4.3. For purposes of illustration, frequencies > 300 observations/patient have been omitted from the figure but were retained for analysis. Heaping is observed at approximately every fourth frequency. This

may be related to the large number of patients with diabetes in this dataset, many of whom may have a regularly scheduled primary care visit every 3 months consistent with current standard of care. Patients without diabetes may be followed less regularly. Weight observation frequencies for subgroups in the study population are shown in Figure 4.4. There are a total of 176,034,543 weight observations for the entire dataset. The highest median number of weight observations occurs in the birth cohorts from 1950-1959, as shown in Figure 4.5. Although the females with diabetes represent the smallest demographic group, the median number of weight observations is higher for this group than from any other, but the maximum number of weight observations is highest in the males with diabetes. The median number of weight observations was higher for patients with diabetes than without diabetes. Some subgroups in some birth cohorts had more than 1000 weight observations (7 of 14 cohorts of females with diabetes, 12 of 14 cohorts of males with diabetes, 4 of 14 cohorts of females without diabetes, and 14 of 14 cohorts of males without diabetes). The median number of weight observations for females with diabetes ranged from 37-49 observations/person across birth cohorts; corresponding statistics for males with diabetes, females without diabetes, and males without diabetes were 22-41, 21-36, and 15-28 observations/person, respectively.

Summary weight statistics by study year, sex, and diabetes status are shown in Tables 4.2-4.5.

4.2 Secular Trends in Body Weight by Birth Cohort

Secular trends in mean body weight are shown in Figure 4.6. During the study period, median body weight was consistently highest in men with diabetes, followed by women with diabetes, men without diabetes, and women without diabetes. Body weight increased linearly in

all groups during the study period. Regression coefficients for secular weight trends over the study period are shown in Table 4.7.

The distribution of weight observations in all groups were heavily skewed, with a wider range of values for the observations above the 75th percentile than the range of values below the 25th percentile, as shown in Figure 4.7. These graphs were generated using PROC SGPANEL using the VBOX option, which plots the minimum, maximum, mean, median, 25th and 75th percentiles, and outliers, according to the SAS online documentation. Peak weights in all groups were at or near the upper boundary allowed value for a valid weight observation, 600 lb (272.16 kg); conversely, minimum weights in all groups were at the lower boundary allowed for valid weight observations, 80 lb (36.29 kg). These findings suggest that the 80-600 lb weight range may be too restrictive to capture the full range of weight variation in the VA population.

Regression equation coefficients for the mean and median for each subgroup by sex and diabetes status are similar, and are shown in Table 4.2.

Further stratification by diabetes status and race was attempted, but only the 1915-1919 cohort was small enough to analyze in this manner in SAS 9.4. The results are shown in Figure 4.8. All weight trends are similar across race categories and diabetes status.

4.3 Longitudinal Trends in Body Weight by Birth Cohort

Penalized b-splines (spaghetti plots) were fit to mean values of the longitudinal data for each patient for the first 100,000 observations in the entire dataset (attempts to fit the entire dataset exceeded available resources). In contrast to the secular trends in mean body weight, the mean longitudinal weight was nearly unchanged during 2000-2014 (data not shown). To rule out the possibility that longitudinal weight trends in some birth cohorts were cancelling out the trends in other birth cohorts, the data were segmented into 5-year cohorts and plotted separately.

Representative spline fits of the mean body weight with 95% CIs for the 1915-1919, 1945-1949, and 1975-1979 cohorts are shown in Figure 4.9. The spline fits show distinctive linear changes in mean body weight following the same patterns as the secular trend, with decreasing body weight in all cohorts born before 1940, nearly stable body weight in all cohorts born during 1940-1949, and increasing body weight in all cohorts born since 1950.

Comparing median body weight at the beginning and ending of the study period within each birth cohort, the progressive changes in the magnitude and slope of the weight change for the 2000 and 2014 timepoints by birth cohort are shown in Figure 4.10. These differences have been replotted as trajectories of the estimated rate of change in median body weight across birth cohorts in Figure 4.11. The trajectories show a highly significant acceleration of body weight change from the oldest to the youngest cohorts in all subgroups by diabetes status and sex (range of R^2: 0.9517 to 0.9881, all $P < .0001$) across the study window, as shown in Table 4.8 and Figure 4.11b.

4.4 A1C Results

A total of 30,769,962 A1C observations in the range 4%-20% were measured in the 1,666,346 patients with diabetes during the 2000-2014 study period. Frequency counts of A1C were obtained and a cumulative probability plot was graphed (Figure 3.2). A total of 14.35% of patients had A1C < 6%, 49.73% had A1C < 7%, and 73.8% had A1C < 8%.

4.5 Smoking Status

Smoking status was obtained for 4,723,383 patients with and without diabetes, which includes patients with birth year before 1915 and after 1984. Using the most logical smoking status classification algorithm developed for this thesis, in which the most recent smoking status was used unless it was contradicted by previously obtained codes, 19% of individuals in the

dataset were current smokers, 58% were former smokers, 19% were never smokers, and 4% had

unknown smoking status.

DISCUSSION AND CONCLUSION

5.1 Discussion of Research Questions

5.1.1 Secular and weight trends

The slopes of the secular trends in body weight over the 15-year period from 2000-2014 reported in this study (Figure 4.5) were similar to those reported by Morgan et al (2012) during 1995-2010, although the baseline weight was approximately 10 kg higher in all subgroups in this study than in Morgan et al. In the current study, the group with the highest mean body weight was the males with diabetes, and the group with the lowest mean body weight was the females without diabetes. However, Morgan et al (2012) found that prevalent and incident females with diabetes had lower mean body weight than the males without diabetes. In the current study, females with diabetes had higher average body weight than males without diabetes.

Obesity prevalence was not calculated in the current study, since the research aims were to assess trends in weight, not BMI. In terms of the larger goals of this study, interventions for type 2 diabetes that affect weight will be explored further. Any potential effects of interventions for type 2 diabetes on height (the other component of BMI) are not foreseen as targets of analysis.

Selecting weight trends for analysis reduces the ease with which results from the current study can be compared with those of population surveys such as NHANES, which typically reports outcomes in terms of BMI. Nevertheless, some NHANES analyses do report body weight outcomes. The secular trends in body weight in the current study were somewhat similar to those observed in NHANES during 2005-2008 and reported by Krieger et al (2013). Both studies found population-wide linear increases in body weight.

An important finding of the current study is that younger birth cohorts had more rapid increases in body weight during the study period than did older birth cohorts. Accelerated weight gain as a function of younger birth cohort is also consistent with the findings reported by Ng et al (2014) in the Global Burden of Disease Study.

The longitudinal pattern of decreasing body weight in older age groups and increasing body weight in younger age groups was previously described by Grinker et al (1995) in the Normative Aging Study, a longitudinal cohort study of more than 2000 men residing in the Boston, Massachusetts metropolitan area. It is unclear whether the statistical techniques used by these investigators to report longitudinal changes in body weight corrected for repeated measures.

Further analysis of data collected from a 646-member subgroup of the Normative Aging Study cohort was performed by Burmaster & Murray (1998). Using a single value of weight for each unique individual in the subgroup, they applied splines fit by LOESS regression to the natural logarithm of body weight as a function of age. Their results show a gradual decrease in ln(weight) from age 50 to age 80. These data are normally distributed, with an ordinary least-squares regression equation with a slope of 0.144 and a y-intercept of 4.410 (R^2 = .996). Using a single value per participant avoids the analytical difficulties associated with repeated measures.

Comparisons between the Normative Aging Study and the current study are facilitated by the facts that both were 15-year studies that divided participants according to 5-year birth cohorts, and the same boundaries were used for each age cohort (Grinker et al, 1995). The subgroup of men without diabetes in the current study was used for comparisons with the participants in the Normative Aging Study, as that is the most nearly comparable subgroup. At study baseline, overall body weight was approximately 10 kg higher in the current study than in the Normative

Aging Study, but the slopes of the trend lines are similar across birth cohorts, as shown in Figure 5.1a.

Longitudinal trends in body weight were also reported in the Normative Aging Study (Grinker et al, 1995). Graphs comparing longitudinal trends in body weight over 15 years in the Normative Aging Study and the current study are shown in Figure 5.1b. Both graphs are plotted to the same scale to facilitate visual comparison. The slopes of graphs by birth cohort follow the same general patterns with age in both studies, but are accentuated in the current study. Baseline weights are consistently higher, and the magnitude of the change in body weight (slope) is consistently larger in the current study.

5.1.2 Discussion of A1C

Individualized glycemic goals represent the current standard of care in type 2 diabetes (Inzucchi et al, 2015). The ADA has a general glycemic target of A1C < 7% for most patients, but notes that a stricter target of A1C < 6% may be appropriate for patients with long life expectancies, short disease duration, no comorbidities or vascular complications, and excellent self-management capabilities. A more relaxed target of A1C < 8% may be appropriate for patients with shorter life expectancies, long disease duration, multiple comorbidities, advanced vascular complications, and limited self-management capabilities. In the current study, a total of 14.35% of patients had A1C < 6%, 49.73% had A1C < 7%, and 73.8% had A1C < 8%. In a VA study of a veteran population aged $\geq$ 75 years, with renal impairment or a diagnosis of cognitive impairment or dementia (N = 652,738), 9.0% of patients had A1C < 6%, 28.6% had A1C < 7%, and 58.4% had A1C < 8% (Tseng et al, 2014).

5.1.3 Discussion of Smoking Status

Numerous inconsistencies were observed relative to smoking status. For example, patients whose most recent smoking status was "nonsmoker" might have prior codes for "current smoker" or "former smoker." Some "former smokers" had prior codes indicating tobacco use. In short, the most recent smoking status was not a reliable indicator of actual smoking history. Other VA researchers have used other strategies for addressing these inconsistencies. For example, Jackson et al (2015) assigned the most frequently cited status as the smoking status. This strategy yields much different proportions of current, former, and nonsmokers than in the current study. In their study of 1,844,797 veterans eligible for the MOVE! lifestyle intervention, 23% of whom had diabetes at baseline, 36% of participants were classified as current smokers, 31% as former smokers, and 34% as never smokers. The "unknown" category was not used.

5.2 Study Strengths and Limitations

5.2.1 Study strengths

This study is notable for being the first to characterize secular and longitudinal trends in body weight in a large, contemporary veteran population from the United States. The dataset includes both men and women, with an age range spanning 70 years. The large size of the dataset—4.68 million unique patients, with 176 million observations of body weight—ensures sufficient statistical power to perform meaningful comparisons between subgroups stratified by sex, diabetes status, race, and birth cohort.

This study is the first published report on secular trends in body weight in male and female veterans with and without diabetes. Because VA data is available to qualified researchers at no cost, these datasets could potentially be used to answer other research questions pertaining to diabetes, obesity, and healthcare utilization.

This dataset includes a large subpopulation of individuals with elevated body weight, with about 25% of the overall population having a body weight between 250-600 lb (113-272 kg); hence, this dataset could be used as a starting point to investigate the correlates of extreme obesity. There is also a large subpopulation of patients with very high rates of weight measurement and primary care utilization, which suggests it may be fruitful as a starting point for healthcare resource utilization research in individuals with and without diabetes.

5.2.2 Study limitations

Some issues related to data quality require resolution. One male with diabetes recorded a total of 10,122 weight observations, an average of 1.8 weight measurements *per day* throughout the 15-year study period. Further investigation is needed to determine whether any of these observations are duplicates, or whether such frequent weight measurements can be clinically justified.

Another data quality issue concerns reported race. Evidently the VA's terminology for reporting race varied during 2000-2014. It is probable that unforeseen variants in the raw response categories may have contributed to the 3% prevalence of missing subjects in the race-stratified analyses. Therefore, caution is warranted when recoding race categories. Gebregziabher et al (2011) proposed a 3-way race classification: black, white, and other, where "other" included all other races as well as unknown, missing, or patients who declined a response.

Due to software limitations and time constraints, none of the analyses performed for the current study accounted for repeated measures of longitudinal data.

5.2.3 Resource limitations

The most important limitations of this study pertain to the analytical resources available through the VINCI platform. Resource limitations, of hardware and software, prevented many of the analyses that were planned for this thesis.

On the hardware side, although 1.1 TB of space appeared to be available on the designated Projects drive, only 100 GB of this space could actually be used, and this partition had to be shared with several other researchers who were also performing large-scale analytics. Of note, the primary analysis file used to answer the questions in Hypothesis 1 occupied 43 GB on disk, and required 20-25 minutes to simply load it from the disk into working memory.

On the software side, the VA's implementation of the 9.4 release of SAS is missing all of the common modeling functions such as PROC REG, GENMOD, and GLIMMIX. Only limited regression capabilities have been retained in SAS 9.4. For example, the REG option was used within PROC SGPANEL to perform spline fitting and linear modeling with 95% CIs to the weight distributions by the year of observation. A number of advanced graphical features used for data visualization, such as contour plots and heat-map style probability density plots, have also been withheld. These functions are now only available in SAS/Grid. The upgrade from SAS 9.3 to SAS 9.4 occurred during fall 2015, while the research for this thesis was being conducted. The loss of functionality from SAS was wholly unanticipated, and the need for familiarization and training on SAS/Grid were outside the scope of the original research protocol.

SAS/Grid is available in the VINCI platform. This implementation of SAS is specifically designed for data mining. Once familiarization and training is completed, this software may resolve the resource issues pertaining to memory, speed, and analytical capabilities encountered using SAS 9.4 on the very large dataset used in the current study. Alternatively, Stata/MP, the multiprocessor implementation of Stata, is also available on VINCI. All implementations of Stata

include the same complete set of features as the others—and this includes different regression models and graphics. Theoretically, Stata/MP can analyze up to 281 trillion observations, although current limitations on hardware memory restrict it to 20 billion observations, with up to 10,998 variables in the models. As a practical matter, the maximum number of observations on VINCI will be limited by the amount of available random-access memory. Further investigation is needed to ascertain whether SAS/Grid or Stata/MP would offer the better choice for future analyses on this dataset.

5.3 Implications of Findings and Conclusions

The hypothesis that body weight would increase with time in all groups depended upon upon which data are reviewed and how they are analyzed:

- Secular trends in body weight increased linearly in men and women with and without diabetes. The magnitude of the weight increase was similar to that observed in a UK population, although in the current study, the females with diabetes weighed more, on average, than the men without diabetes. The US veteran population is approximately 10 kg heavier than the UK population.

- Longitudinal trends show increases in some groups, but not others. Body weight increased during the study period in all cohorts born since 1950, was stable in cohorts born between 1940-1949, and decreased in cohorts born before 1940. These trends were similar regardless of sex or diabetes status. Trends for men without diabetes resembled those of the Normative Aging Study, with higher rates in younger cohorts, but the overall body weights are about 10 kg higher.

The findings of this study are generally consistent with those of other large, longitudinal or cross-sectional studies which also show increases in body weight over time, and faster increases in the rate for younger birth cohorts.

Considering secular trends in body weight, the rates of body weight change in the patients without diabetes are higher than the rates of body weight change in the patients with diabetes—suggesting that future prevalence of diabetes in the VA population will be even higher than it is now. Accordingly, urgent efforts are needed to prevent weight gain in the VA population. The acceleration of weight increase in the younger cohorts suggests that individuals born after 1975 should also be targeted for weight loss interventions.

An unexpected finding of this study is that patients frequently change how they report their smoking history. A novel algorithm based upon the common meaning of the terms current, former, and never smoker was used to classify smoking status. This classification method yields results that differ substantially from those obtained by selecting the most frequently used status as the smoking status. Comparing classification methods would make an interesting potential future thesis topic for an MPH student interested in research methods. The smoking dataset may also be of interest to research investigating changes in smoking status in the VA healthcare system.

Another unexpected finding of this study is that although women with diabetes are numerically the smallest subgroup, they account for the highest number of weight observations on a per-person basis. This study also identified a large number of primary care "superusers," with an average number of weight observations exceeding 1 visit/week for 15 years. These data need to be checked for duplicate records. If they are valid, inquiry could be made to ensure appropriate resource utilization within the VA healthcare system: it would be worthwhile to determine why these groups have higher utilization than other groups.

5.4 Recommendations and Directions for Further Research

Many researchers are engaged in answering questions pertaining to diabetes and obesity. To facilitate future researchers who may search for studies based on this dataset, it is recommended that it be given a name related to its purpose and that can be used as a unique search string when searching online abstract databases such as PubMed. It is proposed that this dataset be named the Veterans Obesity and Diabetes Research Dataset (VODRD) or the Veterans Affairs Diabetes and Obesity Research Dataset (VADOR). The latter acronym has the further advantages of being easy to remember, pronounce, and spell.

5.4.1 Further investigation of hypothesis 1

Survivor bias may account for some of the apparent weight loss in the older cohorts. This could be corrected by reanalyzing the data using 3 of the 12 weight periods, where the endpoints for the weight periods do not overlap. In this manner, only individuals who were alive and had a weight observation in each year of a 12-year period of time would be included in the analysis.

It may be useful for future research on this dataset to determine whether the regression equations described by the coefficients shown in Tables 4.2 and 4.3 are similar. Tests for the equality of regression equation coefficients that are robust to the presence of heteroscedasticity exist (e.g., Toyoda & Ohtani [1986]). For example, it is clear that the women in this dataset generally weigh less than the men, but it is less clear whether there are true differences in the rates of weight change by cohort or year of observation. It would be worthwhile to test for heteroscedasticity in subpopulations of this dataset that may be selected for future analysis.

5.4.2 Further investigations of hypotheses 2-4

Investigation of hypotheses 2-4 will ideally require exclusion of individuals with type 1 diabetes from the dataset. Although patients with known type 1 diabetes are excluded from

enlistment in military service, some veterans may have developed type 1 diabetes after they enlisted. The current study attempts to reduce the number of veterans with type 1 diabetes by restricting the age range. To further reduce inclusion of patients with type 1 diabetes in future analyses, veterans with diabetic ketoacidosis (codes 250.10-13) and BMI < 25 at diagnosis, undetectable C-peptide levels, or detectable GAD antibodies should be excluded.

Consideration should be given to adding variables for treatment facility, height, or BMI to the dataset. These variables would permit the effects of geographically related factors to be removed from the dataset, and would permit stratification of outcomes by BMI.

Propensity score matching is another technique meriting consideration. Propensity score matching can be used to increase the contrast between two interventions, and is considered the next-best thing to a randomized clinical trial.

To date, there is little consensus on the patient characteristics, behaviors, or treatment regimens influencing weight gain with insulin initiation in T2DM. No validated models are available to predict the magnitude or direction of weight change with insulin initiation in T2DM. Published predictive models of weight gain frequently rely upon variables that would not be known at the time of insulin initiation in actual clinical practice. The factors associated with extreme (± 20 kg) changes in body weight within the first year of insulin initiation have not been identified.

To further elucidate the magnitude and direction of weight change with insulin initiation in T2DM, it may be helpful to:

- Develop predictive models based on factors that would be known at the time of insulin initiation in routine clinical practice, and validate these models against a large dataset. Lazarus et al (1998) have previously reported that changes in plasma insulin levels were a

significant predictor of change in body weight (P = .026) in the Normative Aging Study. Similarly, Kloc (2015) found that both insulin sensitivity and insulin secretion can modulate weight gain in a multi-ethnic population of men and women without diabetes.

- Compare groups of patients at the extremes of weight gain or loss at the same time point following insulin initiation to determine whether there are predictable differences in weight gain according to disease characteristics, treatment characteristics, behavioral factors, or laboratory variables.

5.4.3 Significance of Aims 2-4

If this research is performed in its entirety, it will be the first epidemiological study in type 2 diabetes that will investigate the effects of initiating different antihyperglycemic agents on weight change and glycemic control, while controlling for hypoglycemia, physical activity, smoking, and other medications associated with weight gain or loss.

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TABLES

Table 4.1 Demographic characteristics of study population

Characteristic	Total	With Diabetes	Without Diabetes	*P*
Patients, n (%)	4,680,735 (100.00)	1,666,346 (35.60)	2,861,519 (61.13)	
Sex, n				< .0001
Male	4,308,893	1,614,688	2,694,205	
Female	218,972	51,658	167,314	
Race, n				< .0001
White	3,674,044	1,319,478	2,354,566	
Black	672,443	274,189	398,254	
Other	101,914	41,920	59,994	
Unknown	79,514	30,809	48,705	
Missing	152,870	56,417	96,453	
Age,[a] y (mean ± sd)				
White females	70.44 ± 13.44	63.86 ± 13.37	57.58 ± 15.91	< .0001
White males		72.48 ± 10.66	70.07 ± 14.26	< .0001
Black females	63.24 ± 12.84	56.92 ± 10.03	50.48 ± 10.87	< .0001
Black males		66.66 ± 11.00	62.40 ± 13.27	< .0001
Other females	65.58 ± 14.53	58.77 ± 12.16	52.08 ± 13.93	< .0001
Other males		68.88 ± 11.31	64.67 ± 15.74	< .0001
Unknown females	70.03 ± 13.59	63.24 ± 12.77	56.40 ± 15.48	< .0001
Unknown males		71.85 ± 11.00	69.93 ± 14.38	< .0001
Missing females	68.73 ± 13.85	61.45 ± 12.59	55.42 ± 15.11	< .0001
Missing males		70.99 ± 11.10	68.44 ± 14.66	< .0001

[a] In 2014.

Table 4.2 Proportion of population with and without diabetes, by birth cohort and sex

Birth Cohort	Total in Cohort, n	With Diabetes			Without Diabetes		
		F, n	M, n	Total, n (%)	F, n	M, n	Total, n (%)
1915-1919	90,373	470	25,933	26,403 (29.22)	1761	62,209	63,970 (70.78)
1920-1924	313,198	2640	102,719	105,359 (33.64)	7989	199,850	207,839 (66.36)
1925-1929	426,474	847	161,287	162,134 (38.02)	2007	262,333	264,340 (61.98)
1930-1934	498,854	1920	204,404	206,324 (41.36)	3610	288,920	292,530 (58.64)
1935-1939	403,176	2224	173,115	175,339 (43.49)	3967	223,870	227,837 (56.51)
1940-1944	498,171	3793	214,097	217,890 (43.74)	6640	273,641	280,281 (56.26)
1945-1949	906,017	7331	375,013	382,344 (42.20)	13,237	510,436	523,673 (57.80)
1950-1954	471,326	9899	169,552	179,451 (38.07)	21,295	270,580	291,875 (61.93)
1955-1959	325,181	8826	94,883	103,709 (31.89)	25,387	196,085	221,472 (68.11)
1960-1964	213,660	5971	49,839	55,810 (26.12)	23,448	134,402	157,850 (73.88)
1965-1969	138,318	3187	25,587	28,774 (20.80)	16,765	92,779	109,544 (79.20)
1970-1974	92,998	2153	11,587	13,740 (14.77)	14,112	65,146	79,258 (85.23)
1975-1979	72,146	1424	4424	5848 (8.11)	13,248	53,050	66,298 (91.89)
1980-1984	77,973	973	2248	3221 (4.13)	13,848	60,904	74,752 (95.87)
Totals	4,527,865[a]	51,658	1,614,688	1,666,346	167,314	2,694,205	2,861,519

[a] Excludes 152,870 individuals with missing data. Grand total = 4,680,735. DM, diabetes mellitus; F, female; M, male.

Table 4.3 Summary of weight statistics by year of observation, females with diabetes

Wt Year	n	Mean	SD	Median	Q1	Q3	Min	Max
2000	91,493	88.39	19.60	86.64	74.48	100.11	36.29	235.96
2001	125,233	88.70	19.76	86.82	74.84	100.56	36.29	259.19
2002	146,148	89.01	19.98	87.09	74.84	101.10	36.29	264.45
2003	166,959	89.17	20.28	87.09	74.84	101.47	36.29	236.41
2004	188,569	89.38	20.45	87.54	74.84	101.61	36.29	252.43
2005	203,532	89.77	20.72	87.54	75.30	102.06	36.29	249.48
2006	211,196	90.10	20.92	88.04	75.43	102.51	36.29	267.40
2007	222,541	90.23	20.85	88.45	75.66	102.74	36.29	270.00
2008	241,035	90.64	21.11	88.81	75.89	103.10	36.29	268.50
2009	260,055	91.13	21.20	89.13	76.30	103.87	36.29	272.00
2010	257,025	91.35	21.16	89.45	76.52	104.33	36.29	272.00
2011	254,308	91.39	21.11	89.59	76.66	104.33	36.29	264.50
2012	244,067	91.26	21.21	89.36	76.52	104.33	36.29	263.09
2013	231,433	90.96	21.41	89.09	76.20	103.91	36.29	272.16
2014	223,240	88.39	19.60	86.64	74.48	100.11	36.29	235.96

Weight values in kg. Max, maximum; Min, minimum; Q1, 25% quartile; Q3, 75% quartile; Wt Year, year of weight observation.

Table 4.4 Summary of weight statistics by year of observation, males with diabetes

Wt Year	n	Mean	SD	Median	Q1	Q3	Min	Max
2000	2,272,857	96.97	20.08	94.35	83.10	107.96	36.29	272.16
2001	3,196,477	97.16	20.29	94.71	83.10	108.41	36.29	272.16
2002	3,874,723	97.33	20.58	94.80	83.05	108.64	36.29	272.16
2003	4,503,663	97.38	20.88	94.80	83.01	108.86	36.29	272.16
2004	5,022,601	97.45	21.16	94.80	82.92	109.09	36.29	272.16
2005	5,337,943	97.77	21.52	95.26	83.01	109.77	36.29	272.16
2006	5,541,503	98.19	21.91	95.44	83.01	110.22	36.29	272.16
2007	5,686,208	98.60	22.24	95.80	83.19	110.90	36.29	272.16
2008	5,989,368	98.90	21.55	96.16	83.42	111.40	36.29	272.16
2009	6,357,949	99.51	22.66	96.84	83.82	112.13	36.29	272.08
2010	6,254,539	99.79	22.76	97.07	83.92	112.49	36.29	272.16
2011	6,135,949	100.00	22.94	97.30	83.92	112.95	36.29	272.16
2012	5,793,594	100.05	23.08	97.34	83.92	113.04	36.29	272.16
2013	5,486,242	99.91	23.08	97.16	83.82	112.95	36.29	272.16
2014	5,327,701	96.97	20.08	94.35	83.10	107.96	36.29	272.16

Weight values in kg. Max, maximum; Min, minimum; Q1, 25% quartile; Q3, 75% quartile; Wt Year, year of weight observation.

Table 4.5 Summary of weight statistics by year of observation, females without diabetes

Wt Year	n	Mean	SD	Median	Q1	Q3	Min	Max
2000	169,039	75.76	17.47	73.26	63.05	85.73	36.29	238.46
2001	240,441	76.18	17.65	73.66	63.50	86.18	36.29	261.45
2002	285,739	76.40	17.83	73.94	63.50	86.64	36.29	253.11
2003	330,642	76.68	17.89	74.39	63.78	87.09	36.29	262.18
2004	383,278	76.76	13.53	74.39	63.59	87.09	36.29	254.47
2005	421,487	76.90	18.05	74.39	63.87	87.54	36.29	252.15
2006	451,965	77.20	18.24	74.84	63.96	87.91	36.29	267.00
2007	481,901	77.56	18.47	75.30	64.23	88.45	36.29	268.80
2008	533.047	78.01	18.52	75.75	64.64	88.91	36.29	270.00
2009	591,615	78.62	18.58	76.30	65.20	89.68	36.29	263.00
2010	602,800	78.95	18.62	76.70	65.36	90.13	36.29	265.00
2011	614,770	79.33	18.85	77.11	65.77	90.54	36.29	270.00
2012	586,246	79.93	19.09	77.79	66.09	91.22	36.29	266.00
2013	555,680	80.40	19.26	78.34	66.50	91.99	36.29	268.20
2014	540,531	75.76	17.47	73.26	63.05	85.73	36.29	238.46

Weight values in kg. Max, maximum; Min, minimum; Q1, 25% quartile; Q3, 75% quartile; Wt Year, year of weight observation.

Table 4.6 Summary of weight statistics by year of observation, males without diabetes

Wt Year	n	Mean	SD	Median	Q1	Q3	Min	Max
2000	2,511,015	86.16	16.77	84.37	74.84	95.26	36.29	267.44
2001	3,542,600	86.32	16.90	84.46	74.84	95.71	36.29	272.16
2002	4,320,137	86.42	17.07	84.73	74.84	95.71	36.29	272.16
2003	5,092,248	86.36	17.33	84.60	74.84	95.85	36.29	271.70
2004	5,701,941	86.27	17.43	84.37	74.53	95.85	36.29	270.75
2005	6,056,617	86.39	17.69	84.51	74.39	96.16	36.29	272.16
2006	6,286,166	86.71	17.98	84.82	74.57	96.62	36.29	272.16
2007	6,505,014	87.00	18.27	85.09	74.75	97.07	36.29	272.16
2008	6,899,626	87.42	18.53	85.37	74.84	97.52	36.29	272.16
2009	7,435,229	88.09	18.81	86.18	75.30	98.43	36.29	272.16
2010	7,496,083	88.55	18.98	86.50	75.71	99.11	36.29	272.00
2011	7,491,058	88.91	19.21	86.77	75.75	99.66	36.29	272.16
2012	7,027,508	89.12	19.48	87.00	75.75	99.79	36.29	272.00
2013	6,614,960	89.36	19.74	87.09	75.84	100.24	36.29	272.16
2014	6,417,009	89.65	20.06	87.41	75.93	100.70	36.29	272.16

Weight values in kg. Max, maximum; Min, minimum; Q1, 25% quartile; Q3, 75% quartile; Wt Year, year of weight observation.

Table 4.7 Regression coefficients for secular trends in mean and median body weight, by sex and diabetes status, 2000-2014

a. Regression coefficients as calculated

Subgroup		β_1	β_0		
	Outcome	Slope, lb/y	Intercept, lb	R^2	*P*
Females with DM	Mean	0.4895	194.88	0.9046	< .0001
	Median	0.5011	190.58	0.9103	< .0001
Males with DM	Mean	0.5608	212.85	0.9316	< .0001
	Median	0.5286	207.25	0.9260	< .0001
Females without DM	Mean	0.7882	165.58	0.9691	< .0001
	Median	0.8600	159.94	0.9671	< .0001
Males without DM	Mean	0.6082	188.07	0.9118	< .0001
	Median	0.5307	184.36	0.8941	< .0001

DM, diabetes mellitus.

b. Regression coefficients converted to metric units

Subgroup		β_1	β_0		
	Outcome	Slope, kg/y	Intercept, kg	R^2	*P*
Females with DM	Mean	0.2220	88.40	0.9046	< .0001
	Median	0.2273	86.45	0.9103	< .0001
Males with DM	Mean	0.2544	96.55	0.9316	< .0001
	Median	0.2398	94.01	0.9260	< .0001
Females without DM	Mean	0.3575	75.11	0.9691	< .0001
	Median	0.3901	72.55	0.9671	< .0001
Males without DM	Mean	0.2759	85.31	0.9118	< .0001
	Median	0.2407	83.63	0.8941	< .0001

DM, diabetes mellitus.

Table 4.8 Regression coefficients for longitudinal rate of change in median body weight across birth cohorts

a. Regression coefficients as calculated

Subgroup	β_2 Acceleration, lb^2/y	β_1 Slope, lb/y	β_0 Intercept, lb	R^2	P
Females with DM	0.0895	−0.2546	−4.1577	0.9517	< .0001
Males with DM	0.0398	0.3362	−4.4998	0.9760	< .0001
Females without DM	0.0127	0.6616	−4.8949	0.9861	< .0001
Males without DM	0.0260	0.4462	−3.9000	0.9881	< .0001

DM, diabetes mellitus.

a. Regression coefficients converted to metric units

Subgroup	β_2 Acceleration, kg^2/y	β_1 Slope, kg/y	β_0 Intercept, kg	R^2	P
Females with DM	0.0406	−0.1155	−1.8859	0.9517	< .0001
Males with DM	0.0181	0.1525	−2.0411	0.9760	< .0001
Females without DM	0.0058	0.3001	−2.2203	0.9861	< .0001
Males without DM	0.0118	0.2024	−1.7690	0.9881	< .0001

DM, diabetes mellitus.

FIGURES

Figure 3.1 Data selection flowchart
a. Data selection for weight analyses

** 0.09% of observations were < 80 lb;
< 0.01% were > 600 lb
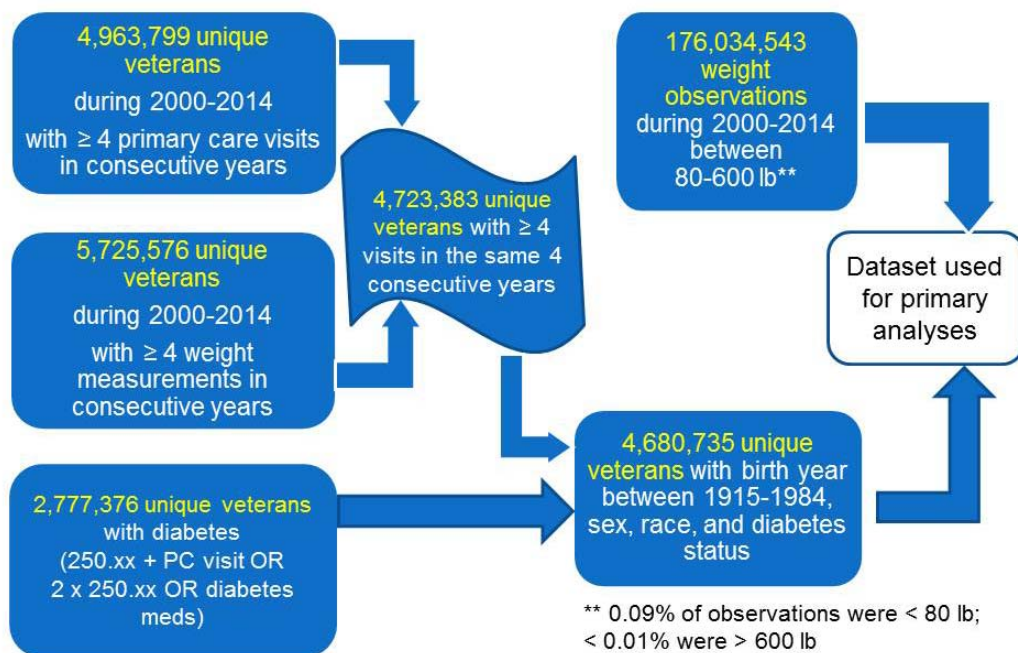
b. Data selection for Hypotheses 2-4
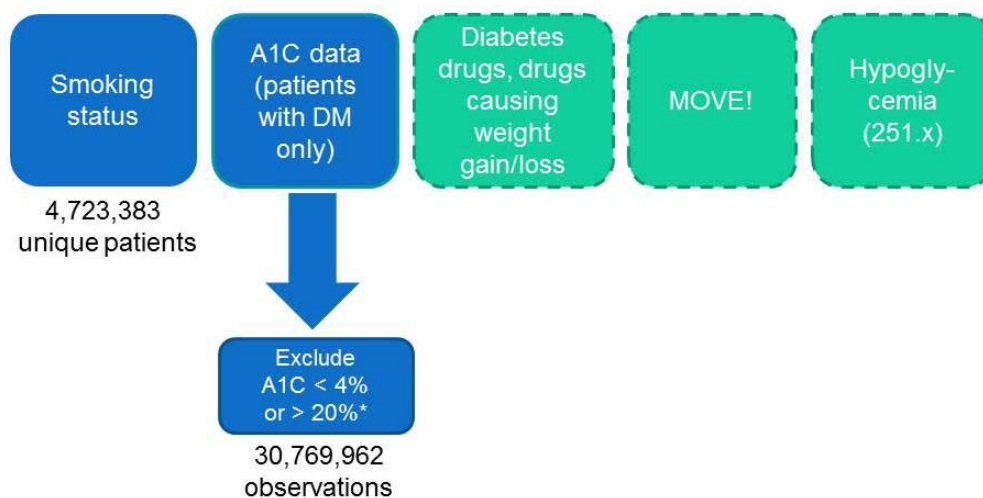
* 0.03% of all observations were < 4.0%;
< 0.001% were > 20%

Dark blue boxes and arrows indicate processes used to prepare data for this thesis. Light blue arrows indicate processing to be performed in the future. Green boxes indicate data to be pulled in the future.

Figure 3.2 Raw A1C data—cumulative probability
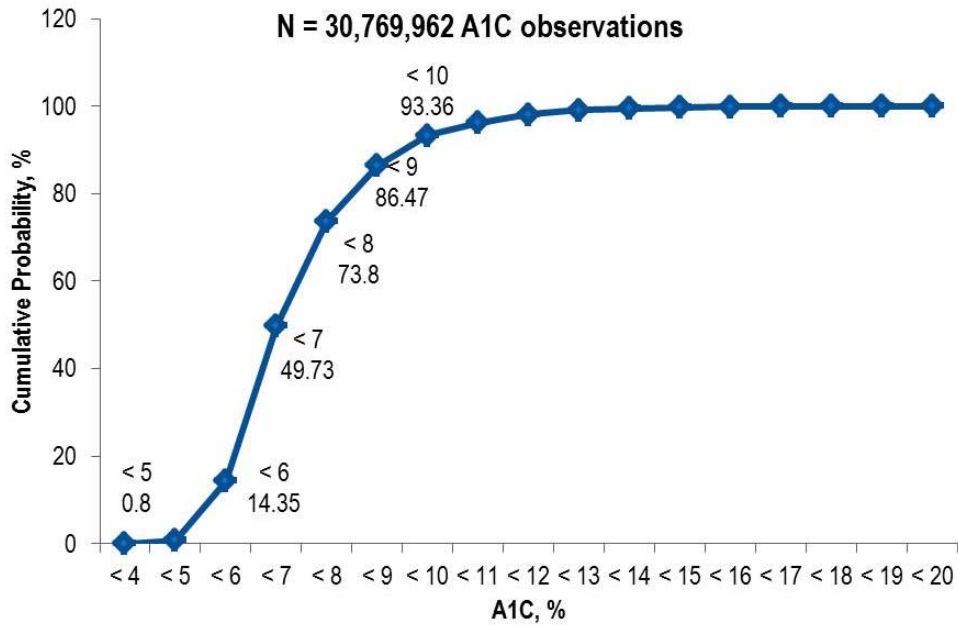
Figure 4.1 Distribution of patients by race, sex, and diabetes status
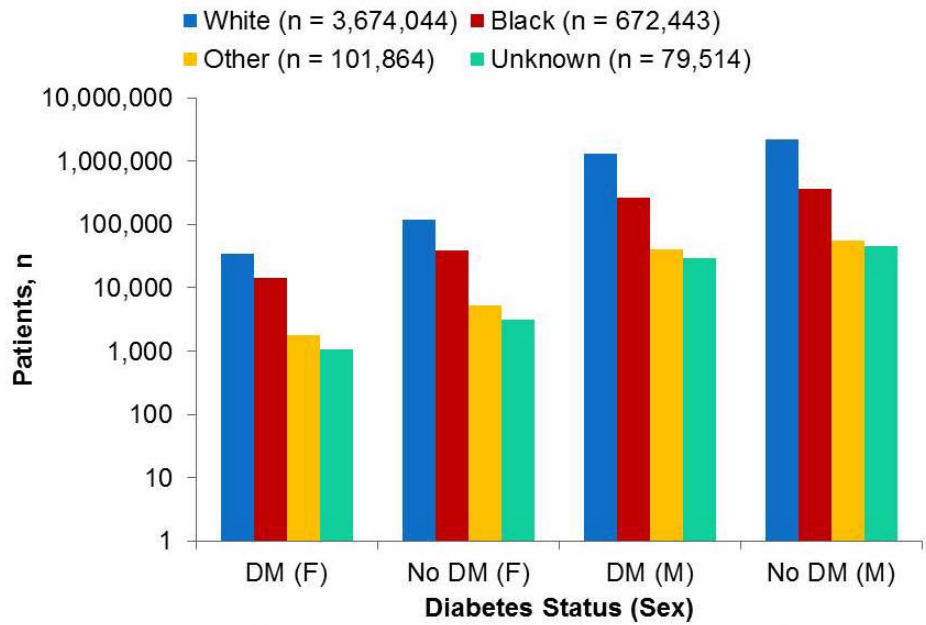
4,680,735 patients in the entire dataset; 152,870 missing.

Figure 4.2 Distribution of unique patients by birth year
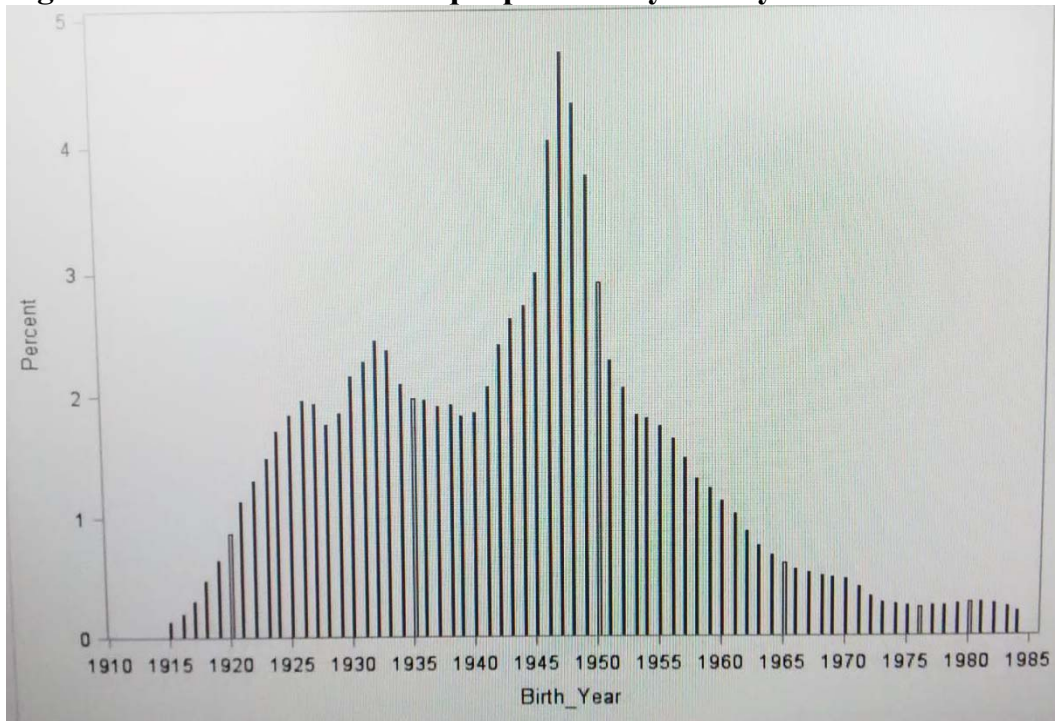
4,680,735 patients in the entire dataset; 152,870 missing.

Figure 4.3 Distribution of weight observations by frequency
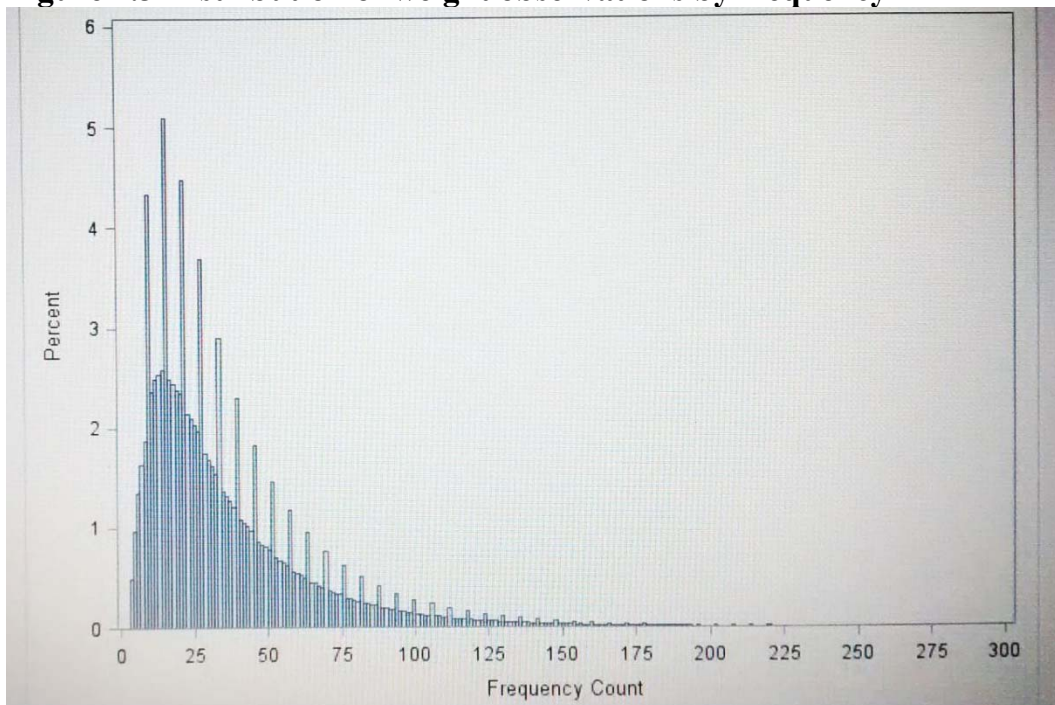
Figure 4.4 Distribution of weight observations by diabetes status, sex, and birth cohort
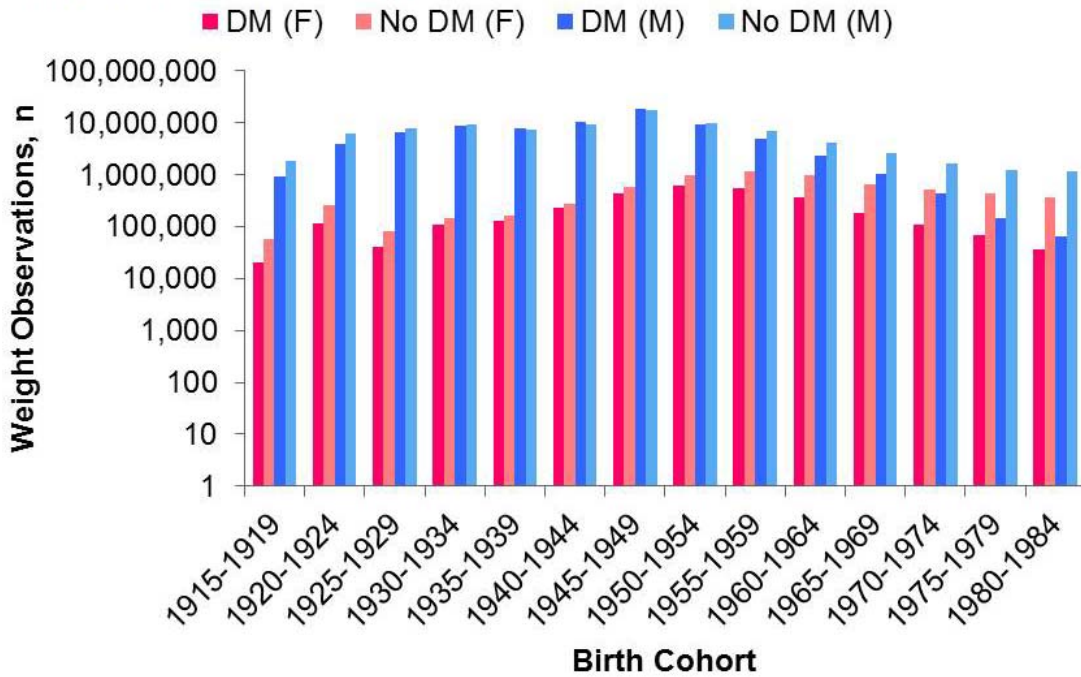
176,034,543 weight observations for the entire dataset. DM, diabetes mellitus; F, female; M, male.

Figure 4.5 Distribution of median number of weight observations per patient by diabetes status, sex, and birth cohort
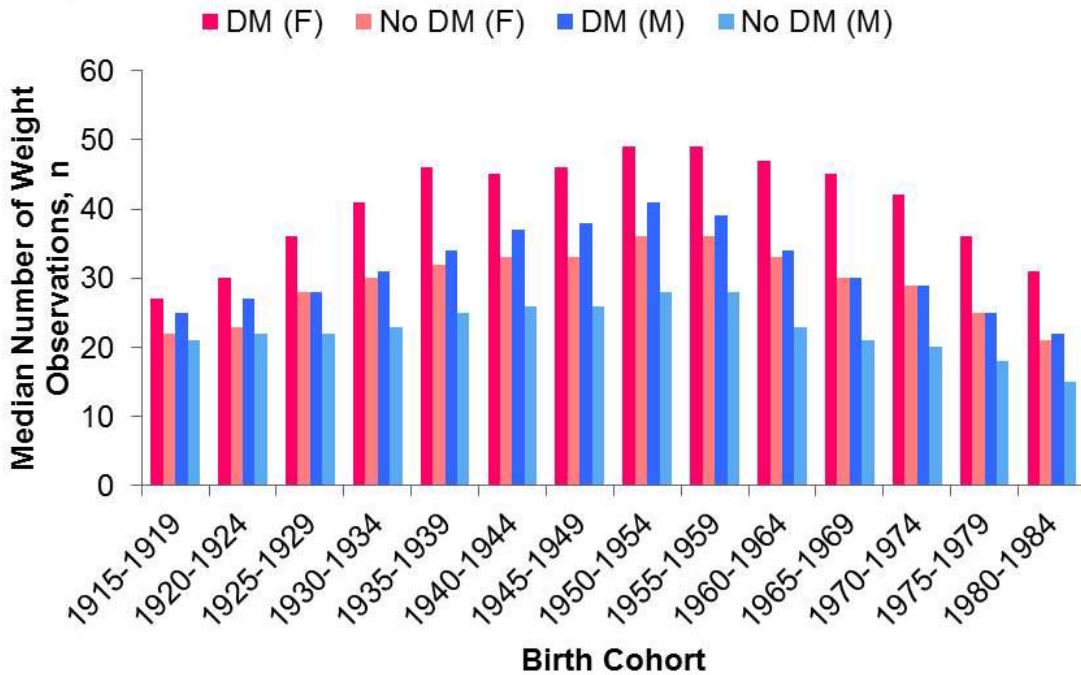
176,034,543 weight observations for the entire dataset. DM, diabetes mellitus; F, female; M, male.

Figure 4.6 Secular trends in mean body weight by year, sex, and diabetes status
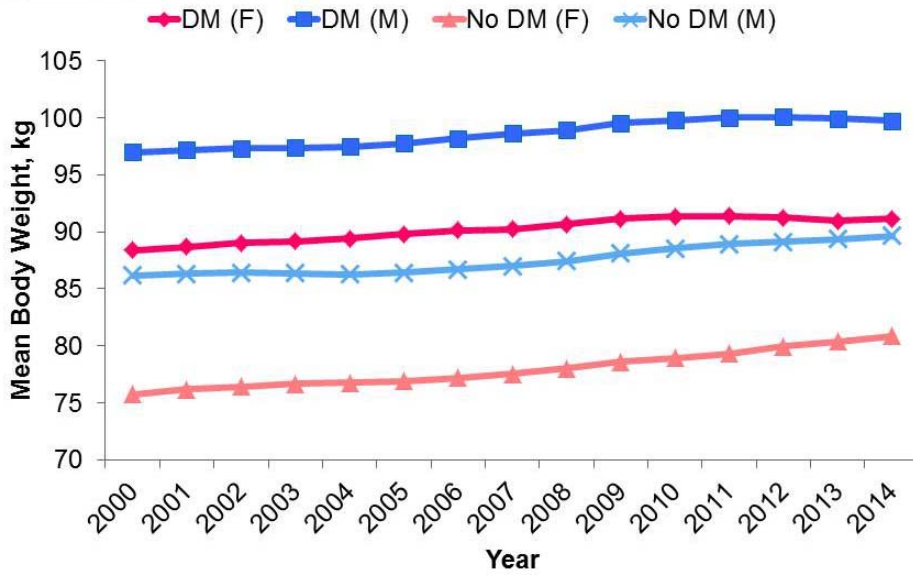
DM, diabetes mellitus; F, female; M, male.

Figure 4.7 Distribution of weight observations by sex and year of measurement in selected cohorts
a. 1915-1919 cohort
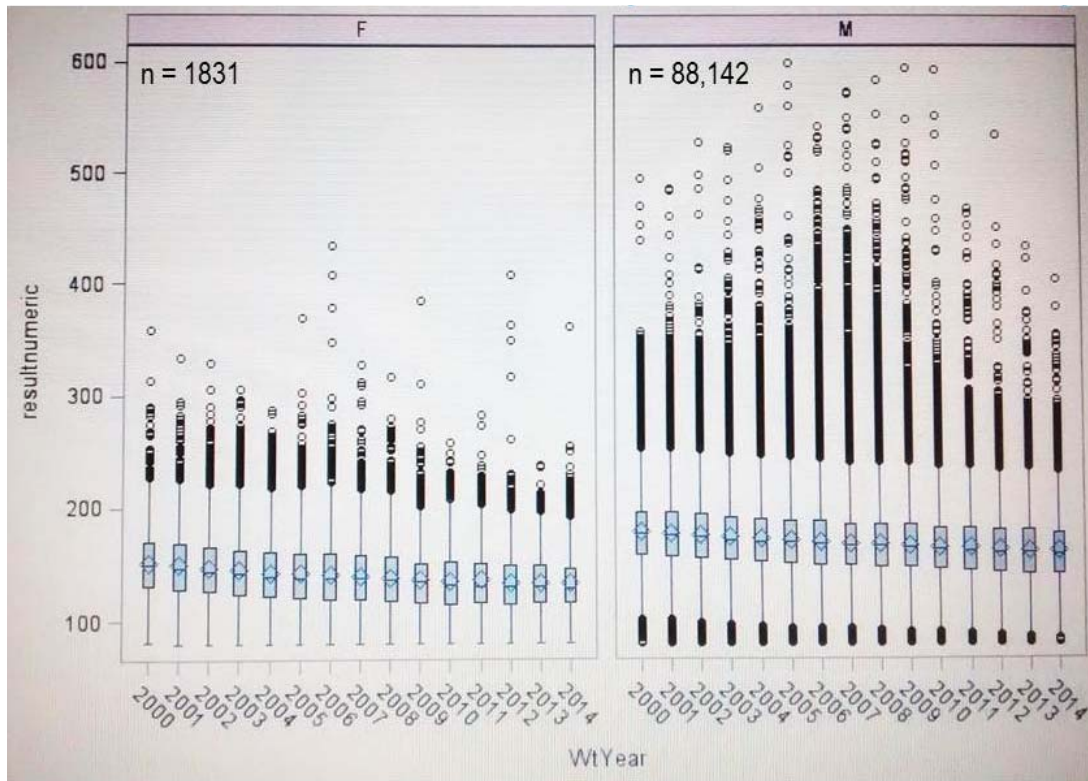
b. 1945-1947 cohort[a]
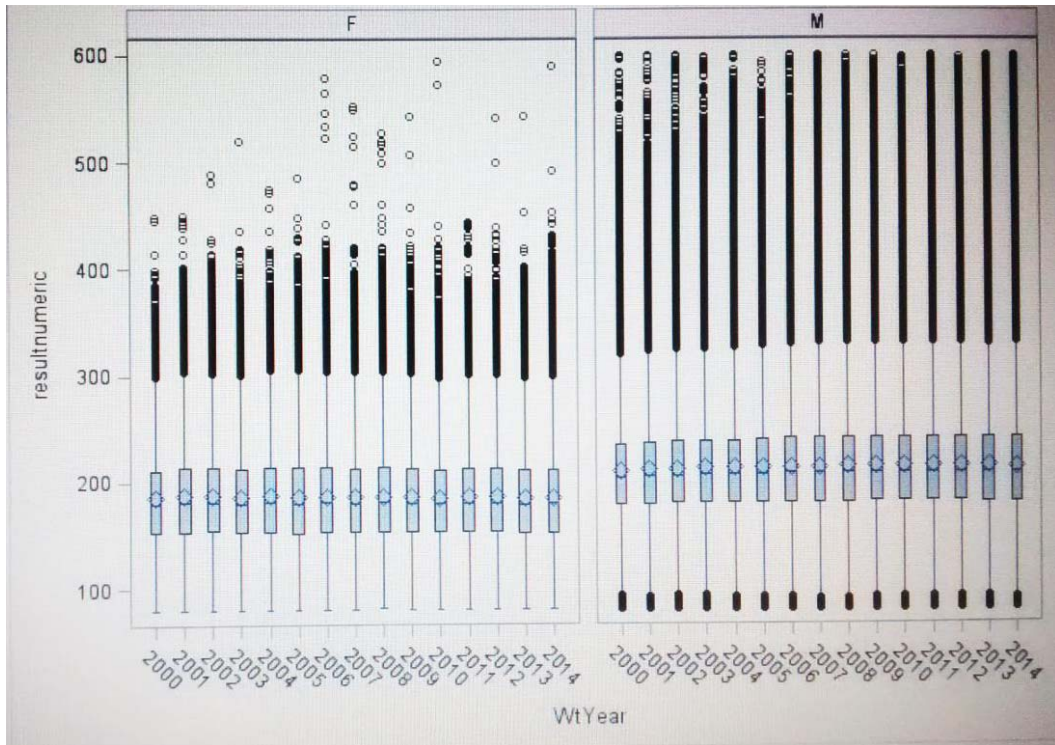
c. 1975-1979 cohort
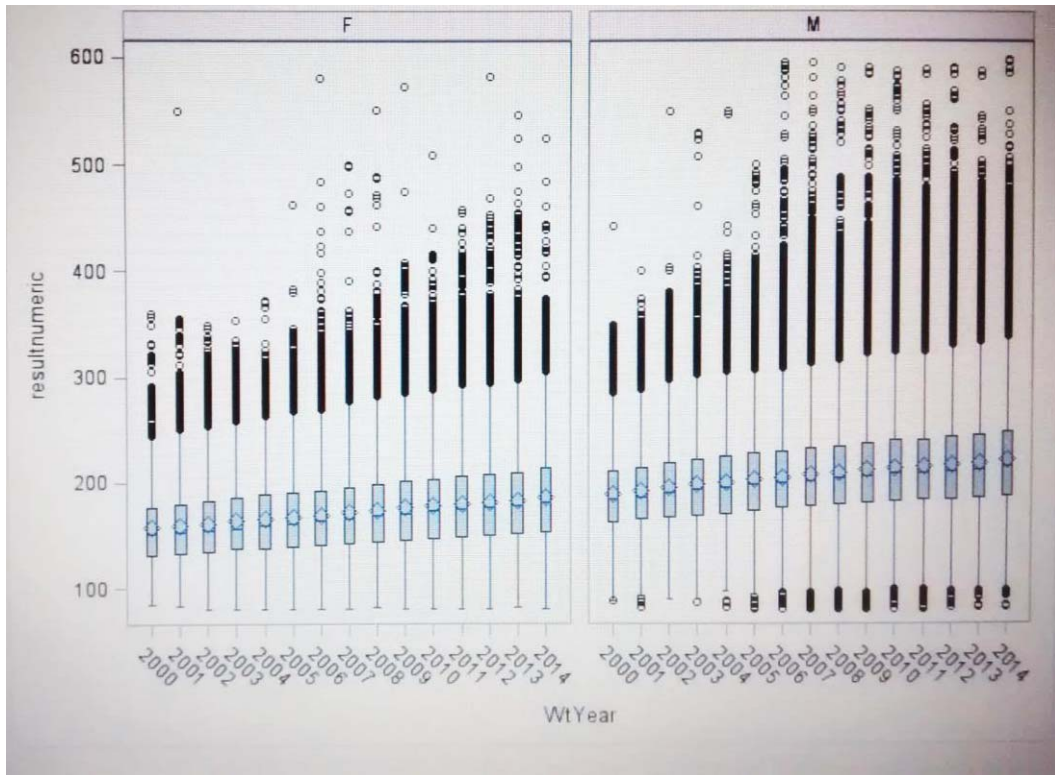
F, female; M, male; resultnumeric, weight (lb).

Because of the large number of individuals with birth years between 1945-1949 (906,017 individuals; 20,568 females, 885,447 males) caused memory overflow errors in SAS 9.4, a 3-year cohort (1945-1947) was computed.

Figure 4.8 Secular trends in the distribution of weight observations by race, diabetes status, and year measured, 1915-1919 birth cohort

a. Patients with diabetes

b. Patients without diabetes

Distribution of Weight Observations by Race and Year Measured (1915-1919 Cohort)
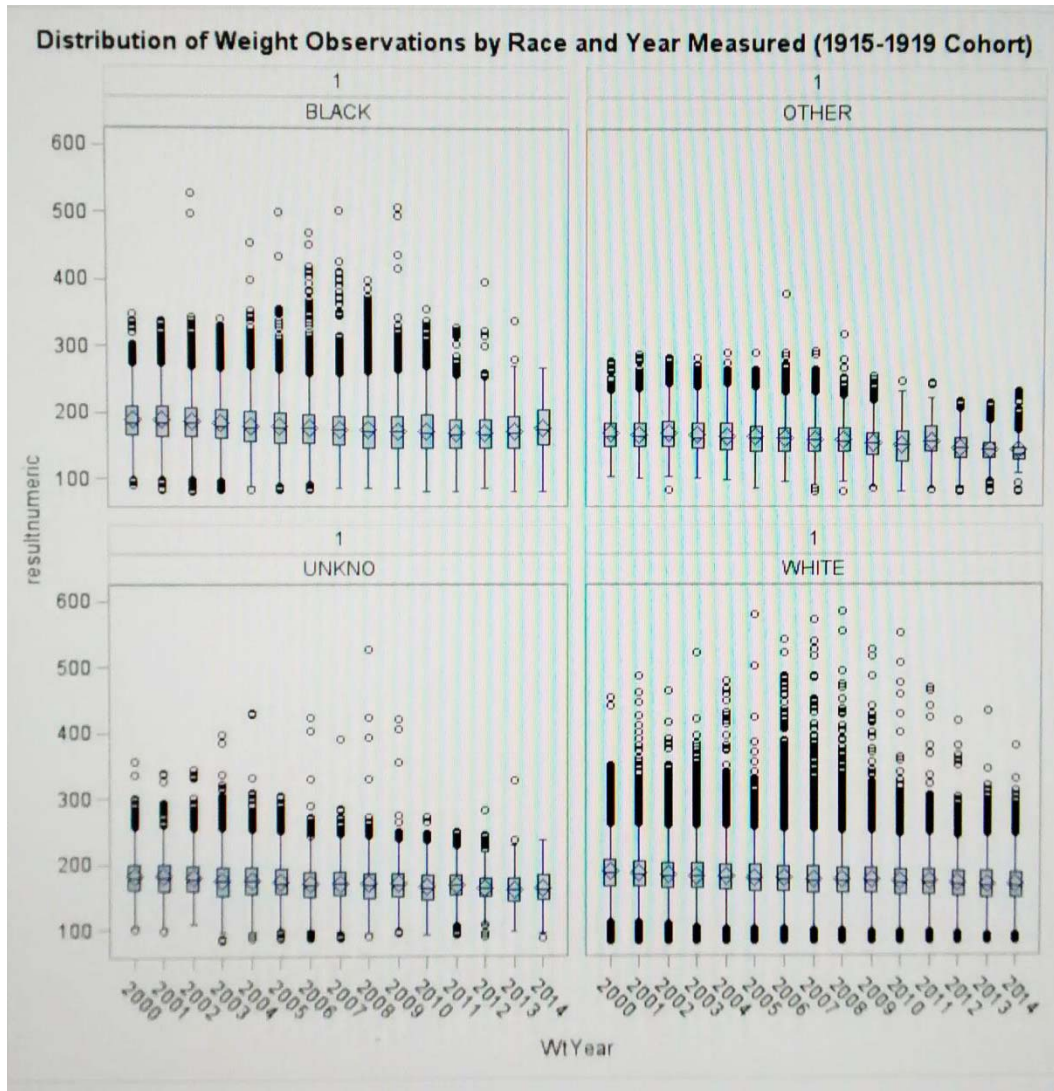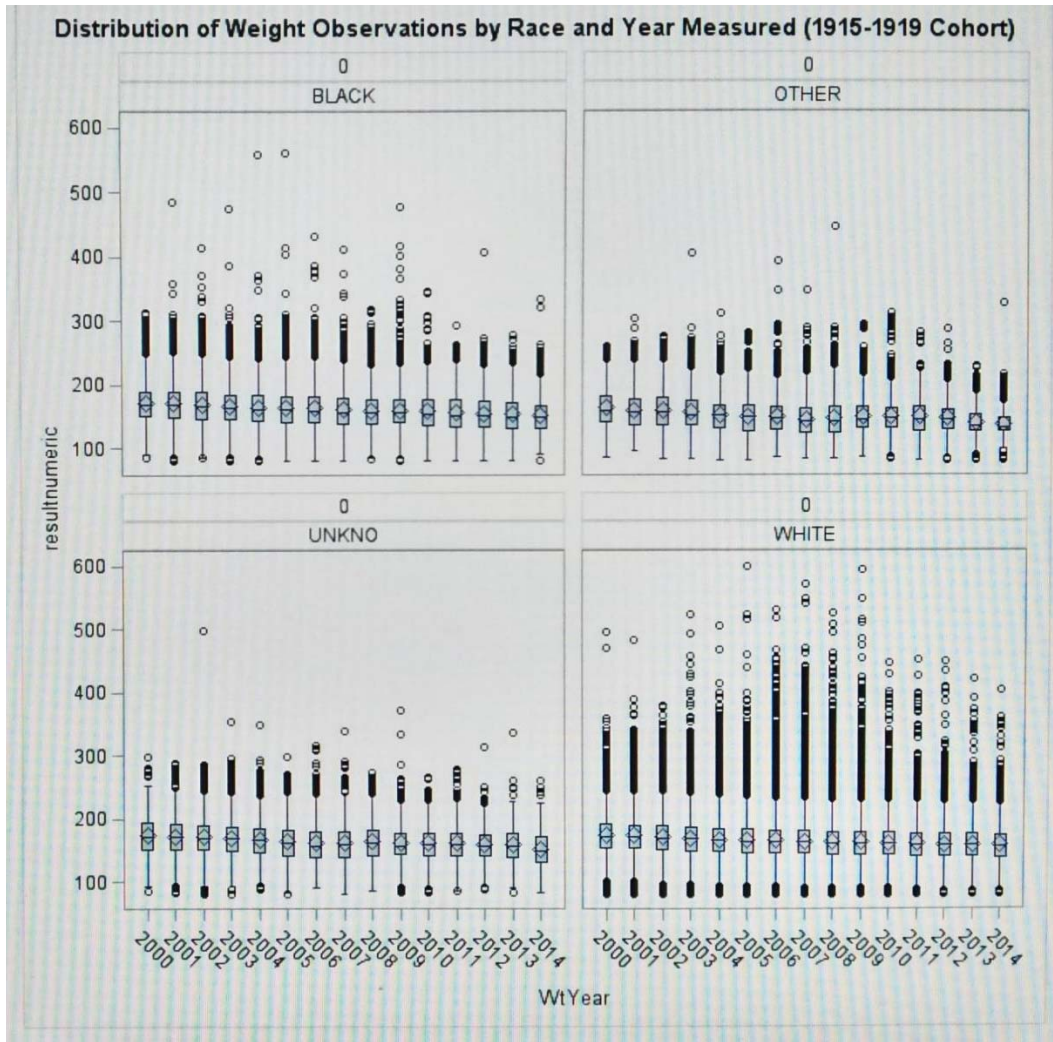
0, no diabetes; 1, diabetes; resultnumeric, weight (lb); Unkno, unknown.

Figure 4.9 Representative longitudinal spline fits for mean body weight with 95% CIs, 2000-2014
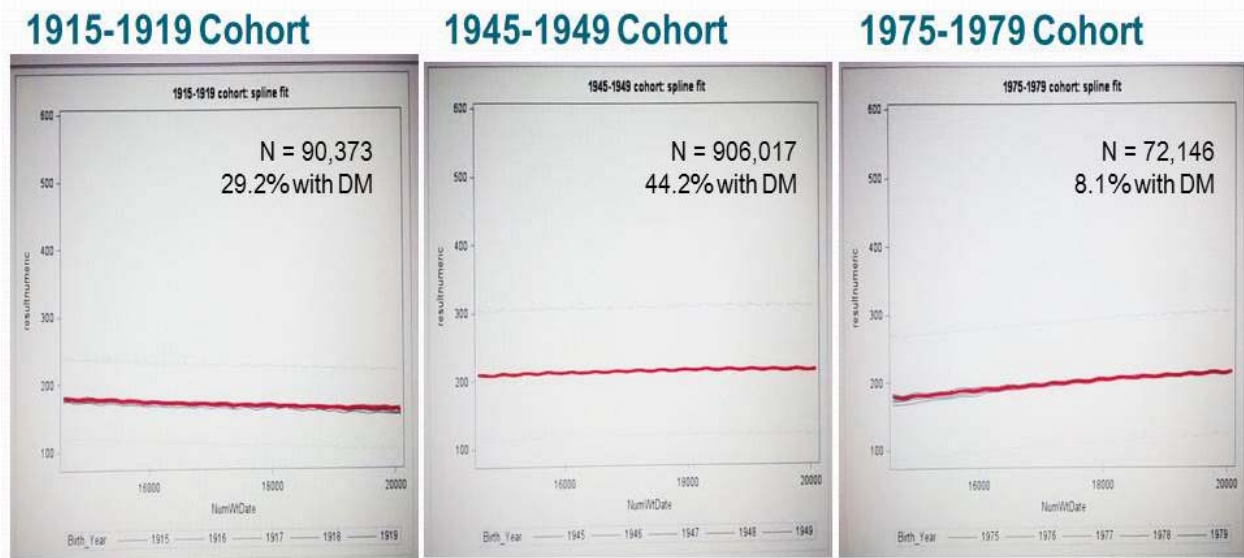
N, number of unique individuals in cohort; NumWtDate, numeric weight date (x-axis minimum = 2000; x-axis maximum = 2014); resultnumeric, weight (lb). Data shown have not been corrected for repeated measures.

Figure 4.10 Changes in median body weight by birth cohort, 2000 and 2014
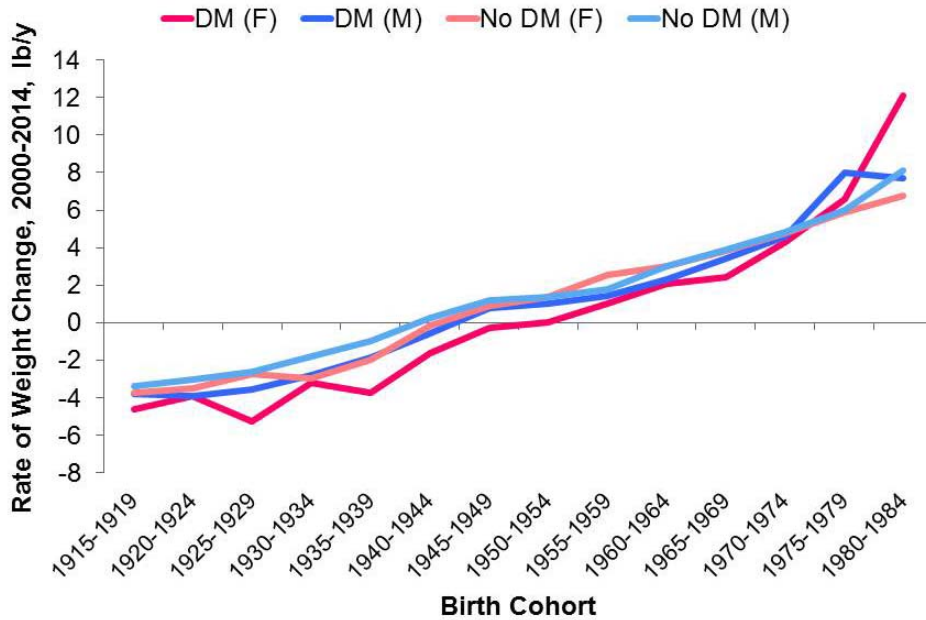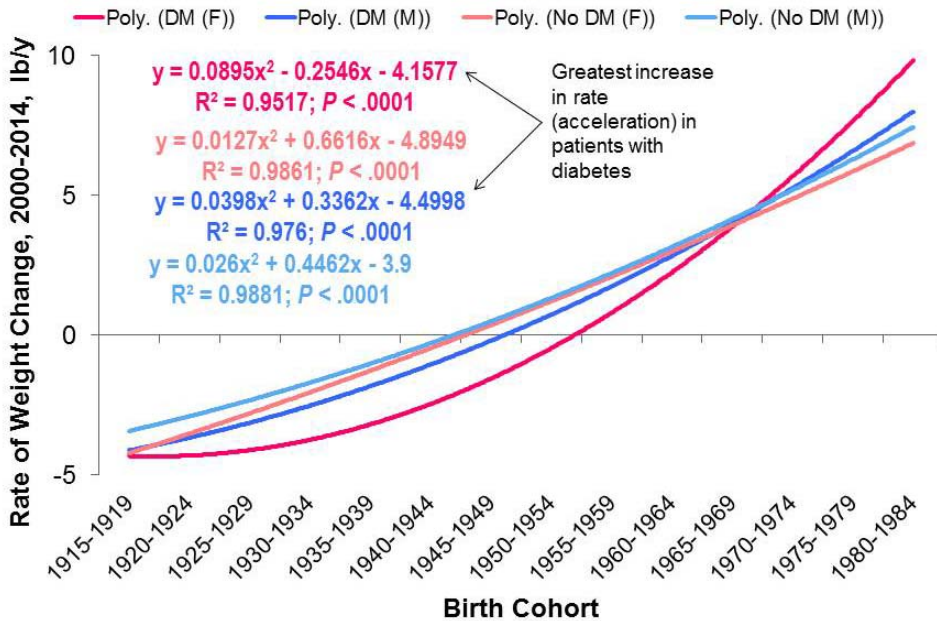
a. Females
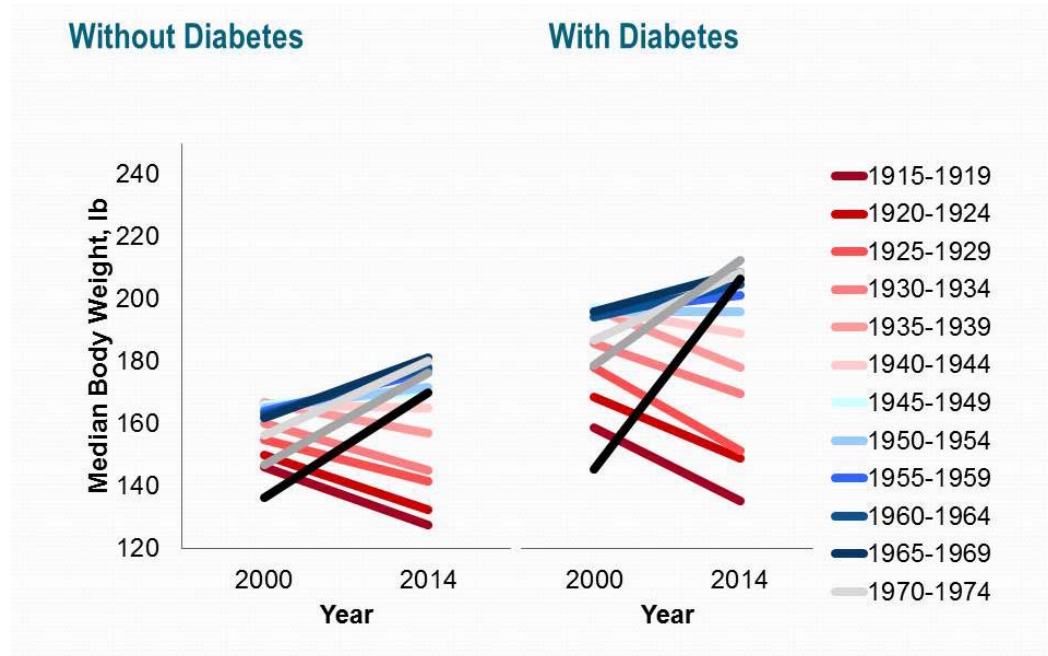
b. Males
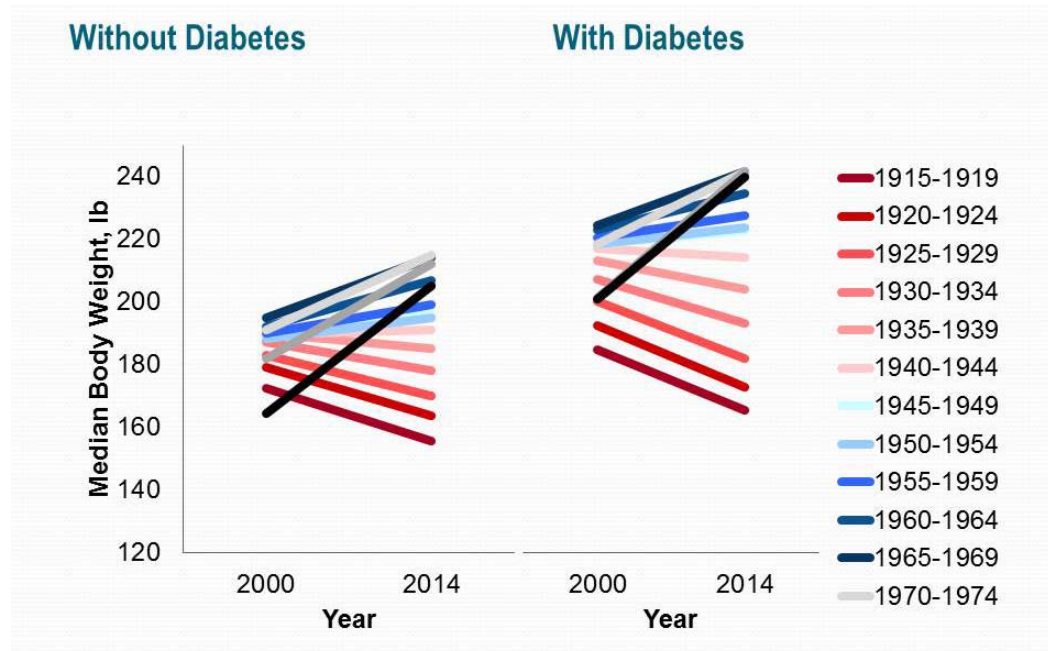
Figure 4.11 Trajectories of rate of change in median body weight by sex, diabetes status, and birth cohort, 2000 and 2014

a. Crude rate—calculated from difference in the median body weight in 2000 and 2014
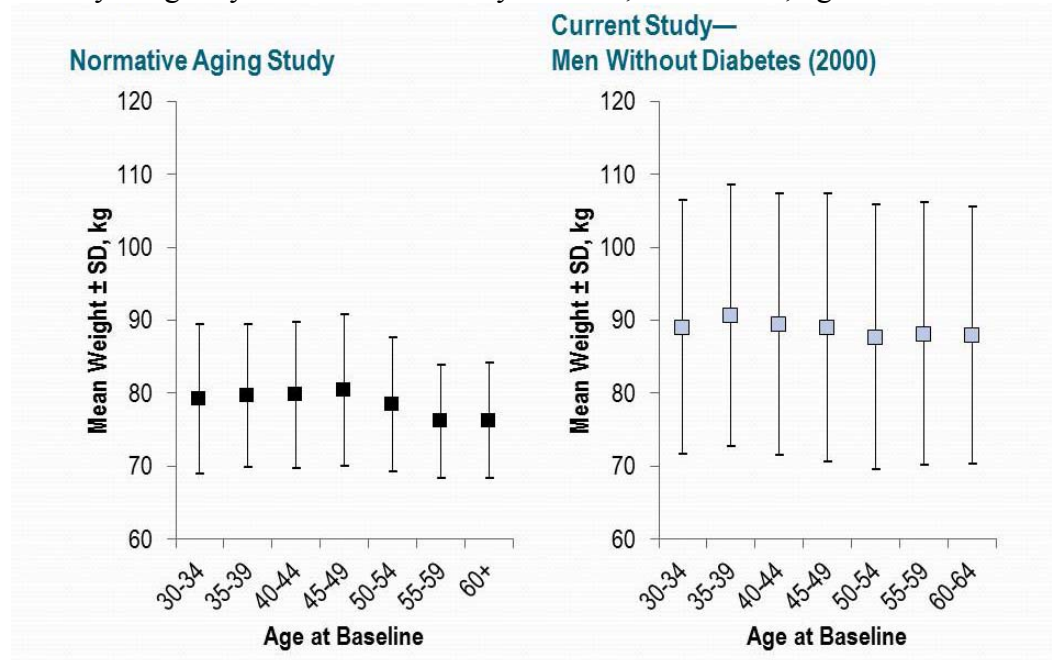

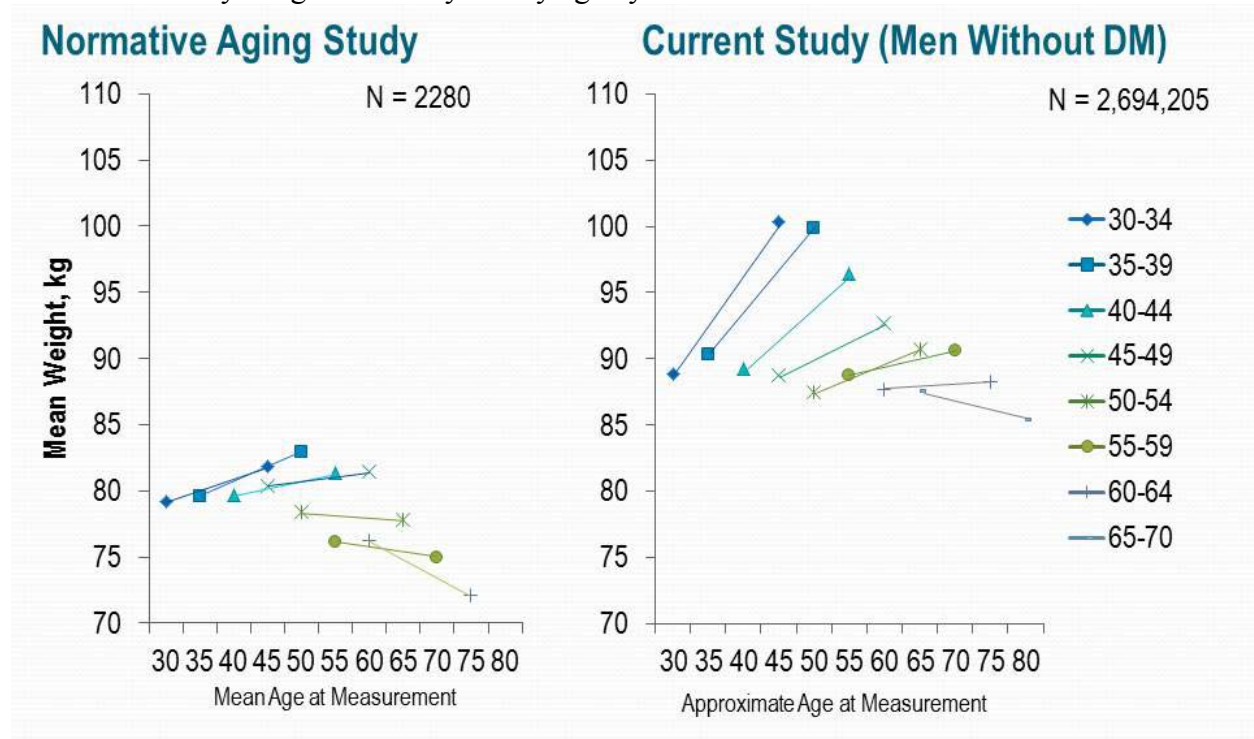b. Estimated rate—least-squares second-order polynomial

DM, diabetes mellitus; F, female; M, male.

Figure 5.1 Baseline differences and longitudinal changes in body weight by birth cohort—comparisons with Normative Aging Study (Grinker et al, 1995)

a. Body weight by birth cohort at study baseline, mean ± SD, kg

b. Trends in body weight over 15 years by age by birth cohort

DM, diabetes mellitus. Data for Normative Aging Study from Grinker et al (1995). Legend shows age at baseline.

APPENDICES

Appendix 1. Clinical Trial Acronyms

ACCORD, Action to Control Cardiovascular Risk in Diabetes

ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation

CREDIT, Cardiovascular Risk Evaluation in People With Type 2 Diabetes on Insulin Therapy

ORIGIN, Outcome Reduction with Initial Glargine Intervention

VADT, Veterans Affairs Diabetes Trial