Adiposity and Mortality in Type 1 Diabetes

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Abstract

Background—In the general population, adiposity exhibits a J- or U-shaped relationship with mortality; however, in catabolic states this relationship is often inversely linear. We have recently documented an age-independent increase in overweight/obesity in the Pittsburgh Epidemiology of Diabetes Complications study (EDC) of type 1 diabetes (T1D). As intensified insulin therapy (IIT) may promote weight gain, the impact of weight gain in T1D is of importance. We therefore assessed the association of adiposity with mortality in 655 EDC participants during twenty years of follow-up.

Methods—Individuals were categorized as underweight (BMI <20), normal (20 ≤BMI<25), overweight (25 ≤BMI<30), or obese (BMI ≥30). Cox models were constructed using BMI and
covariates at baseline, updated means during follow-up, time-varying (reflecting most recent status), and change during adulthood as predictors of mortality.

**Results**—The prevalence of IIT (3+ insulin shots daily and/or pump) increased from 7% to 82%. Overweight increased 47%; obesity increased 7-fold. There were 146 deaths. In unadjusted models BMI (modeled continuously) demonstrated a quadratic relationship with mortality (p=0.002, <0.0001, <0.0001 for baseline, updated mean, and time-varying models, respectively). However, only in the time-varying model were the obese significantly different from the normal weight. while the baseline model revealed no differences by BMI category, in both the updated mean and time varying models, the underweight were at greater risk than the normal weight (p<0.0001 both models). The nonlinear relationship of adiposity with mortality remained after adjustment for diabetes complications, biological, or socioeconomic/lifestyle risk factors, with the exception of baseline socioeconomic/lifestyle risk factors where a linear association emerged. Adjustment for waist circumference eliminated the risk in the obese. Finally, weight gain during follow-up was protective.

**Conclusion**—The relationship of adiposity with mortality in T1D now appears to resemble that of the general population, albeit with a marked increased risk in those underweight.

Mortality in type 1 diabetes (T1D) is greatly accelerated, occurring several decades earlier than in the general population (1–5). Although adiposity is associated with increased risk of many chronic diseases in the general population (6–9), there is some evidence that this relationship may not be so straightforward, particularly for mortality, where U- and J-shaped relationships are often observed (10–14). Furthermore, within diseased populations, increased adiposity is often associated with longer survival (15–17).

Within type 1 diabetes, coronary artery disease (CAD) is the leading cause of death overall, although renal disease, especially at shorter and medium term durations of diabetes, is also a major contributor (1, 18, 19). Chronic complications such as these are part of the natural history of type 1 diabetes and thus may confound the relationship of adiposity with mortality. Furthermore, in T1D the association of overweight and obesity with mortality may be further complicated, as intensive insulin therapy is associated with both weight gain and a reduction in complications.

Few studies have fully investigated adiposity as a risk factor for mortality in T1D. In the studies in which it has considered, adiposity was not been demonstrated to be a risk factor for mortality (19–21), with the exception of Roy et al (22) in which adiposity was associated with longer survival. However, with the marked increase in overweight and obesity, and therefore a much wider range in adiposity, in T1D this situation may be changing. This paper investigates the association of adiposity with mortality above and beyond the known risk factors for mortality in T1D. To both serve the needs of the practicing clinician and to account for confounding and address reverse causation, adiposity is investigated as both a baseline predictor and as a function of BMI change over an 18–20 year time period.
Methods

The Pittsburgh Epidemiology of Diabetes Complications Study is a prospective study based on a well-defined cohort of individuals with childhood-onset (<17 years old) type 1 diabetes mellitus. There were 658 eligible subjects (325 women and 333 men; 98% Caucasian) diagnosed between January 1, 1950, and May 30, 1980, who were first seen between 1986 to 1988; 654 provided BMI and some follow-up data. Mortality follow-up was censored January 1, 2008.

At biennial cycles of examinations, information was collected concerning demographic characteristics, medical history, and health care behaviors as previously described (23, 24). At each cycle, both a standardized medical history and clinical examination were performed by a trained internist to document complications of diabetes.

Participants were weighed in light clothing and without shoes on a balance beam scale. Height was measured using a stadiometer. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. For the first ten years of follow-up, all height and weight were measured. Beginning in 1998, exams were limited to certain subgroups, so measured height and weight data were not fully available until 2004–2007, when an eighteen year follow-up exam was again made available to all participants. Self-reported data from the medical history questionnaire were used when measured data were not available, representing 83% and 33% of the data from the 12th and 16th year follow-up periods, respectively. The validity of the reported height and weight has been reported (25). Underweight was defined as a BMI < 20kg/m^2; normal weight as 20 kg/m^2 ≤ BMI < 25 kg/m^2; overweight as 25 kg/m^2 ≤ BMI < 30 kg/m^2; obesity as BMI ≥ 30 kg/m^2. Weight change was defined as BMI at the 10-year follow-up exam minus baseline BMI.

Fasting blood samples were assayed for lipids, lipoproteins, glycosylated hemoglobin (HbA1), creatinine, and hematocrit. High-density lipoprotein (HDL) cholesterol was determined by a heparin and manganese procedure, a modification (26) of the Lipid Research Clinics method (27). Cholesterol was measured enzymatically (28). Stable glycosylated hemoglobin A1 (HbA1) was originally measured in saline-incubated samples by microcolumn cation exchange chromatography (Isolab, Akron, Ohio, USA). On October 26, 1987, the method was changed to high-performance liquid chromatography (HPLC) (Diamat, Bio-Rad Laboratories, Hercules, CA, USA). The two methods were highly correlated (r = 0.95). Beginning in 1998, HbA1c was measured using the DCA2000 analyzer. Original HbA1 (1986 to 1998) and A1c (1998 to 2004) were converted to Diabetes Control and Complications Trial (DCCT) aligned HbA1c values using regression formulas derived from duplicate analyses (DCCT HbA1c = [0.83 * EDC HbA1] + 0.14; DCCT HbA1c = [EDC HbA1c − 1.13]/0.81). Blood pressure was measured by a random-zero sphygmomanometer according to a standardized protocol (29) after a 5-minute rest period. Blood pressure levels were analyzed, using the mean of the second and third readings. Insulin dose/kg body weight was defined as the total daily units of insulin divided by the body weight in kilograms.
Intensive insulin therapy was defined as having three or more insulin injections per day or using an insulin pump. Physical activity was determined by number of flights climbed per day, city blocks or equivalent walked per day, and mets calculated from sports/exercise*minutes of participation*number of times per week, and is expressed in kilocalories. Complications were assessed as previously described (23, 24) and overt nephropathy (ON) defined as albumin excretion rate >200 µg/min in 2 of 3 timed urine samples (30) or a history of renal dialysis or transplant. All procedures were approved by the Institutional Review Board of the University of Pittsburgh.

Statistical analyses

The student’s t test and chi-square tests were used to examine univariate associations of BMI category with mortality risk factors. Cox proportional hazards modeling was used to determine the independent predictive ability of BMI category on mortality, with normal weight being used as the reference. Risk factors were grouped into three categories (complications, biological risk factors, and socioeconomic/lifestyle risk factors) and models fitted separately for each group as predictors of mortality. The number of participants included in different statistical models varied due to item nonresponse. Preliminary analyses revealed that the relationship of BMI category with mortality was essentially similar in each sex; therefore sex-specific analyses were not conducted. Children younger than 18 years old (n=66) were excluded from baseline analyses. Cox models with baseline risk factors were used to determine the association of baseline BMI category on mortality. Cox models with updated mean covariates were also used to determine the association of average BMI status during follow-up with mortality. The updated mean was determined by taking the average value of a risk factor during follow-up. For dichotomous variables, the updated variable was entered as the number of years with the given risk factor. The forward selection procedure was used to identify the most predictive risk factors; BMI category was forced into all models. Cox models with time-varying covariates were used to determine the association of most recent BMI status with mortality. To account for the colinearity between BMI and waist circumference, the residuals of BMI regressed on waist circumference were used in models incorporating waist circumference. Finally, Cox modeling was also used to determine the association of the residuals of weight change with mortality in adults at least 18 years old at baseline. Variables are expressed as per standard deviation change in the continuous variable. All tests were two-tailed and a p-value <0.05 was considered significant. All analyses were conducted using SAS version 9.1 (Cary, North Carolina).

Results

Body mass index data were available on 655 participants and 99.8% (654) provided some follow-up data. Participants (mean age and diabetes duration 28 and 19 years, respectively) were followed for a median of 18.2 years (range: 0.2–20.6 years). There were 146 deaths (22%).

Baseline characteristics of the participants (aged 18 years and older) by BMI category are described in Table 1. At baseline, compared to normal weight participants, obese participants had a higher non-HDL cholesterol. Overweight participants also had, compared
to normal weight, a lower HbA1c, were on more insulin injections per day, had a higher diastolic blood pressure, a lower HDL cholesterol, a lower prevalence of symptomatic autonomic neuropathy, and were less likely to be current smokers.

During follow-up, the prevalence of intensive insulin therapy (IIT-3+ insulin shots daily and/or pump) increased from 7% to 82% (25). The prevalence of being overweight increased by from 28.6% to 42.0% while the prevalence of obesity increased 7-fold (from 3.4 to 22.7%) over an average of 18 years of follow-up (25). Figure 1 shows the unadjusted association of mortality with baseline BMI category (panel a), updated mean BMI status during follow-up (panel b), and most recent BMI status prior to event or censoring (panel c). Baseline BMI demonstrated a slight U-shape relationship with mortality (p for quadratic term=0.002), such that there was a higher risk in the underweight relative to the normal weight and a more marked higher level of risk in the obese. However, average BMI during follow-up (updated means model), revealed a reverse J-shaped relationship with mortality, such that those with an average BMI in the obese category were at slightly increased risk of mortality relative to the normal weight, but the greatest risk was in those with an average BMI less than 20 kg/m² (p for quadratic term <0.0001). The BMI nadir for mortality risk fell in the overweight category. In the time-varying model, reflecting most recent BMI status prior to event or censoring, the risk in the underweight and obese appeared to be even stronger, compared to the baseline and updated means models, with the risk in the underweight being 3 times, and the risk in the obese twice, that of the normal weight (p for quadratic term<0.0001).

The results of modeling baseline risk markers according to type, namely, complications, biological risk factors, or socioeconomic/lifestyle risk factors are shown in Table 2. As sample size with full data available varies for these three risk marker categories, the base models show the relationship of BMI category with mortality, specific for that population, adjusted only for age and sex. The increased risk in the obese was attenuated after adjustment for chronic complications of diabetes, and eliminated after adjustment for biological and socioeconomic risk factors. The multivariable baseline models thus showed weak U- and J-shaped relationships with mortality.

Table 3 shows the relationship of updated mean BMI category with mortality. In contrast to the baseline model, average BMI status during follow-up demonstrated a strong U-shaped relationship with mortality even after adjustment for the proportion of follow-up time spent with complications. Adjusting for these complications did not account for the increased risk in the underweight or obese. Similarly, compared to the base model, adjusting for updated mean biological risk factors had very little effect on the BMI relationship with mortality. However, adjusting for socioeconomic lifestyle risk factors, including intensive insulin therapy which emerged as a protective factor, eliminated the risk in the underweight while no substantial change in risk of the obese was noted.

Table 4 shows the relationship of most recent BMI status with mortality. Adjusting for time-varying complication status appears to attenuate the risk in the underweight compared to the base model, while adjusting for time-varying biological or socioeconomic/lifestyle risk factors does not appear to have substantial affect the relationship of BMI category with
mortality. Compared to the baseline and updated means models, whether adjusting for complications, biological risk factors, or socioeconomic/lifestyle risk factors, base and adjusted time-varying models show a stronger (larger effect size) adverse relationship with being underweight.

The Spearman correlation between BMI category and waist circumference at baseline was 0.68 (p<0.0001). When age and sex adjusted waist circumference was modeled instead of BMI, baseline waist circumference was an independent predictor of mortality (HR 1.33, 1.11–1.60, p=0.003) however, updated mean waist circumference demonstrated a U-shaped relationship with mortality (p=0.0002). Similar results as the updated mean were obtained for the time varying analysis (p=0.009 for age and sex adjusted quadratic term). To determine if this relationship of waist circumference with mortality accounted for the relationship of excess BMI with mortality, the residuals of BMI regressed on waist circumference were added to the model with age and sex adjusted waist circumference. Baseline waist circumference remained an independent positive predictor of mortality (HR=1.43, 1.19–1.72, p=0.002) while baseline BMI residuals showed an inverse relationship with mortality (HR=0.84, 0.76–0.93, p=0.0008). The relationship of updated mean waist circumference remained quadratic (p=0.0004) and, as in the baseline model, the residuals of updated mean BMI remained inversely associated with mortality (HR=0.88, 0.80–0.97, p=0.01). Similar results to those seen in the updated means models were observed in the time-varying model, i.e. waist circumference demonstrated a quadratic relationship with mortality (p=0.004), while BMI was inversely associated with mortality (HR=0.90, 0.83–0.98, p=0.01).

Figure 2 shows the association of change in BMI in adults during the first ten years of follow-up with mortality during years the subsequent 10 years. BMI change ranged from −6.5 to 11.0 kg/m². There was a significant trend for a positive change in BMI to be associated with a lower mortality, such that for each tertile of change, risk was reduced by approximately one-third (p for trend=0.01). In multivariable analysis in adults 18 years and older, after controlling for baseline BMI, age, and albumin excretion rate, and allowing for intensive insulin therapy and other univariate significant risk factors, each one unit positive change in the residuals of BMI change during the first 10 years of follow-up was associated with a 12% decreased risk of mortality during follow-up years 11–20 (HR=0.88, 0.80–0.97) (Table 5). When this analysis was repeated stratified by a BMI less than 25 kg/m², similar results were obtained for the normal/underweight (HR=0.79, 0.69–0.92, n=225) and the overweight/obese (HR=0.88, 0.75–1.04, n=101), although the effect was stronger for those with a BMI less than 25 kg/m² (p-value for interaction =0.0003) (data not depicted).

**Discussion**

In this report, we have documented the association of both baseline BMI and BMI measured repeatedly during follow-up with mortality in type 1 diabetes. To our knowledge, this is the first study to document the long term association of adiposity with mortality in type 1 diabetes, where adiposity was the predictor of interest. We have shown that baseline BMI demonstrated a slight U-shaped relationship with 20-year mortality. We have also shown during follow-up the role of underweight as a predictor increases and conversely, we have
shown that weight gain in adults with type 1 diabetes is protective against mortality. Finally, we have shown that the role of overweight and obesity in increasing mortality appears to be largely mediated by waist circumference.

The relationship of BMI with mortality in this population was not linear, neither at baseline nor throughout follow-up. Although Roy et al (22), found BMI to be inversely associated with mortality (HR=0.94, 0.91–0.97) in a large African American population with type 1 diabetes, in general in type 1 diabetes the relationship of BMI with mortality has been reported to be nonsignificant, although apart from the present study, no study has specifically looked at mortality in this population with BMI as the explanatory variable of interest. The association of BMI with mortality in the general population is usually found to exhibit a U-or J-shaped curve, although some argue that this may be due to failure to exclude for pre-existing disease, smoking, or recent weight loss (31–33). Against this, others have shown that even after excluding for pre-existing disease, smoking, or recent weight loss, this non-linear relationship persists (13, 34, 35). Excluding for pre-existing disease in type 1 diabetes may be debatable, as type 1 diabetes itself is a pre-existing disease. Furthermore, 55% of our adult population at baseline, with a mean age of 29, had at least one of the long-term diabetes complications at study entry and 23% of our adult population at baseline were smokers; therefore, exclusion of smokers and those with pre-existing disease would not be representative of the type 1 diabetes population. However, we have attempted to account for weight loss, smoking, and long-term complications by looking at them biennially in updated means and time-dependent survival analyses. In our population, after examining the association of BMI on mortality with up to twenty-years of follow-up, BMI failed to show a linear relationship with mortality, demonstrating a similar relationship to that observed in the general population, with the exception of a much increased risk in those whose average or most recent BMI was in the underweight category.

Untreated type 1 diabetes is a wasting disease, characterized by severe deficiency or absolute absence of the anabolic hormone, insulin, essential to ensuring intake of energy into cells and the prevention of muscle and fat catabolism. Without this hormone, the natural history of the disease would be a progressive wasting to death. Upon correction of wasting via exogenous insulin, an alternate natural history commences. This alternate natural history includes progressive kidney disease, with its sequelae of hypertension leading to further progression of kidney disease leading to an atherogenic lipid profile, anorexia, and wasting in its final stages. This alternate natural history also includes very early cardiovascular disease, autonomic neuropathy with its dysphagia, anorexia, and early satiety, other neuropathies causing muscle wasting or limited mobility via pain, bone deformities, or amputations. It includes blindness, with its limitation on mobility, and peripheral vascular disease, the latter also causing limited mobility due to pain or amputations. Finally, this natural history ends with very early mortality, with its obvious limit on the time in which weight gain can occur and its implications for adiposity as in populations with limited longevity increased adiposity tends to be protective. Any effects of or on adiposity within type 1 diabetes must take place within this environment and to the extent that these effects mirror the general population, whether good or bad, these represent a major accomplishment in type 1 diabetes.
A major biologic risk factor for mortality in our population was HbA1c. HbA1c has been shown previously to be a risk factor for mortality in type 1 diabetes (1, 36) and Shankar et al (36) noted that the mortality risk associated with HbA1c was greater at a higher BMI although this was not noticed by Stadler et al (1). In this population, both HbA1c and intensive insulin therapy were positive predictors of weight gain (25, 37); however, in the prediction of mortality, while HbA1c was directly predictive, average amount of time spent on intensive insulin therapy during follow-up was protective. We have thus shown a complex interaction between catabolic and anabolic factors over the approximate two decades of follow-up. Intensification of insulin therapy increased dramatically while HbA1c, a marker of glycemic control, showed a substantial reduction, both factors directly associated with weight gain via a reduction in catabolic tissue breakdown and glycosuria and an increase in adipose tissue storage. They are also indirectly associated with weight gain via a reduction in complications associated with wasting, i.e. nephropathy and autonomic neuropathy (38). Nevertheless, although the progression of the natural history of the disease has slowed, it has not halted, and for coronary artery disease, little improvement has been made (3), and after 18 years of follow-up, the EDC population is considerably older with considerably more complications and thus the wasting process may still be operant.

The effect of change in weight over time is another dimension of the complex association of adiposity with mortality in type 1 diabetes. In adults eighteen years and older, we observed a protective effect of weight gain, as assessed by BMI, and mortality, such that with each increasing tertile of change, mortality was reduced by approximately thirty-three percent. While it is not unexpected for weight loss to predict mortality in a population with pre-existing disease, i.e. type 1 diabetes itself, we found that weight gain had beneficial survival effects beyond that of even the relatively weight stable, an observation that should be underscored as average baseline BMI in this population was 23.8 kg/m², a value well within the normal weight range. Weight change modeled as a continuous variable was inversely associated with mortality even after adjustment for other factors associated with mortality. Although weight gain in adulthood has been reported to be a positive predictor of mortality (35) and that weight loss is beneficial if volition is taken into account (39, 40), in the main, general population studies have demonstrated an inverse or U-shaped relationship between weight change and mortality (41–43), even when pre-existing illness and smoking have been taken into account (44, 45). In our population with type 1 diabetes, with a mean age of 29 years at baseline, weight gain also appeared to be protective against mortality in middle-age.

A major observation of this study was that waist circumference accounted for the U-shaped relationship of BMI with mortality. Some have hypothesized that, contrary to being due to a failure to adequately control for smoking, subclinical, or occult disease, the non-linear relationship observed between BMI and mortality may be a consequence of BMI being a composite of both fat and fat-free mass (46–48), not simply a surrogate for overall adiposity. Bigaard et al (48) demonstrated that the U-shaped relationship between BMI and mortality was due to the J-shaped relationship of fat mass and the reverse J-shaped relationship of fat-free mass with mortality. Several studies have shown that adjustment for waist circumference, a surrogate for abdominal adiposity (49–52), eliminates or attenuates BMI’s nonlinear relationship of with mortality (53, 54). In our type 1 diabetes population as well, adjustment for waist circumference also eliminated the U-shaped relationship between BMI
and mortality and the relationship became inversely linear. Beyond suggesting that the effect of obesity on mortality is largely mediated through central adiposity, this is suggestive of a protective effect for both peripheral body fat and for lean body mass. Consistent findings have also been reported in the literature (46, 55, 56).

Strengths and Limitations

Major strengths of our study include the prospective nature of the design, measured height and weight, repeated assessment of height and weight as well other risk factors over time, and a long follow-up period. As BMI was assessed every two years, we were able to assess the affects of weight change on mortality, demonstrating an increased risk in those who lost weight and a decreased risk in those who gained the most weight, a weight gain well beyond a normalization of weight.

A major strength of this paper could also be one of its limitations. As this study tracked mortality over 20 years, changes in both diabetes treatment and risk factor management associated with obesity may have affected mortality results. However, we have attempted to account for this, as well as weight change, in the time-varying covariate models. Results from these models did not reveal a major change in the association of obesity with mortality, but a they did reveal a much stronger relationship with being underweight and a reversal of the relationship of being overweight with mortality, even after long-term diabetes complications and intensive insulin therapy were taken into account. This would seem to suggest that with improved diabetes treatment and risk factor management, a modest increased adiposity is actually beneficial, as also suggested by our analysis of weight change.

Conclusion

With the rise in overweight and obesity in type 1 diabetes, and the rise in intensive insulin therapy, the traditional view of type 1 diabetes as a starvation state is clearly outdated. Nevertheless, an interaction between catabolic and anabolic imbalances is evidenced by the increased risk in the obese and the greatly increased risk in the underweight. Although an understanding of the risk associated with obesity is of interest, in terms of a disease traditionally characterized by relative thinness and enhanced catabolism, of greater concern maybe the excess mortality risk due to leanness. Given the wide BMI range associated with minimal mortality (20–29 kg/m²), weight gain is not necessarily a bad occurrence in type 1 diabetes. Though frank obesity should be avoided, risk factor management may be better focused on glycemia, blood pressure and lipids, and other complication specific risk factors, than on overweight per se.

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Figure 1.
Risk of Mortality by Body Mass Index (BMI) Category
Figure 2.
Mortality by in Adults during years 11–20 of Follow-up by change in Body Mass Index (BMI) during the first 10 years of Follow-up (n=475)
Table 1

Baseline (1986–1988) Characteristics by BMI Category in Adults 18 Years and Older (mean ±SD), % (n), or median (IQR)

| Characteristics                          | BMI <20 | 20≤BMI<25 | 25≤BMI<30 | BMI ≥30 | p-trend |
|------------------------------------------|---------|-----------|-----------|---------|---------|
| Sex (female), %                          | 57.6 (34)| 49.7 (171)| 42.8 (71) | 70.0 (14) | 0.37    |
| Age (years)                              | 30.2±6.2| 29.1±7.1  | 28.8±6.5  | 28.8±6.9 | 0.39    |
| Diabetes Duration (years)                | 21.3±6.2| 20.3±7.4  | 20.3±6.9  | 21.3±7.3 | 0.99    |
| BMI (kg/m²)                              | 19.1±0.81§| 22.7±1.3  | 26.9±1.4§ | 31.6±1.7§| <0.0001 |
| **Biological risk factors**              |         |           |           |         |         |
| HbA1 (%)                                 | 8.8±1.7 | 8.8±1.5   | 8.4±1.3§ | 8.6±1.1 | 0.24    |
| Daily insulin dose/kg body weight        | 0.82 (0.59–0.99) | 0.75 (0.58–0.91) | 0.77 (0.63–0.93) | 0.74 (0.63–0.90) | 0.11 |
| Insulin injections per day               | 1.5±0.50 | 1.6±0.83  | 1.8±1.0§ | 1.9±0.85 | 0.01    |
| Intensive insulin therapy (%)            | 0.0 (0)  | 6.8 (22)  | 9.4 (15)  | 10.5 (2) | 0.02    |
| Systolic blood pressure (mm Hg)          | 109.2±17.7 | 114.5±16.8 | 117.4±14.0 | 118.6±16.5 | 0.01 |
| Diastolic blood pressure (mm Hg)         | 70.1±12.3 | 72.7±10.7 | 76.6±10.6§ | 76.4±12.0 | 0.005 |
| Hypertension (%)                         | 13.6 (8) | 17.4 (60) | 19.4 (32) | 30.0 (6) | 0.12    |
| HDL cholesterol (mg/dL)                  | 55.9±13.3 | 54.8±13.0 | 51.1±11.6§ | 50.4±8.4 | 0.03    |
| Non-HDL cholesterol (mg/dL)              | 128.8±35.0 | 137.1±40.8 | 146.7±47.2 | 162.2±47.4§ | 0.0007 |
| AER * (µg/min), median (IQR)             | 31.6 (11.9–178.5) | 17.4 (7.3–241.4) | 22.7 (9.4–297.9) | 42.2 (5.8–423.8) | 0.65 |
| WBC (×10³/mm²)                           | 6.7±2.2  | 6.6±1.9   | 6.7±1.9   | 7.7±2.3 | 0.05    |
| **Complication, %**                      |         |           |           |         |         |
| Coronary Artery Disease                  | 8.5 (5)  | 8.5 (29)  | 8.4 (14)  | 5.0 (1) | 0.78    |
| Overt Nephropathy                        | 27.8 (15) | 29.9 (96) | 33.3 (50) | 42.1 (8) | 0.20    |
| Proliferative Retinopathy                | 39.0 (23) | 32.1 (106) | 41.1 (65) | 42.1 (8) | 0.24    |
| Symptomatic Autonomic Neuropathy         | 10.9 (5) | 11.3 (31) | 3.7 (5)§ | 6.3 (1) | 0.04    |
| Distal Symmetrical Polyneuropathy        | 46.4 (26) | 32.6 (104) | 32.4 (48) | 36.8 (7) | 0.26    |
| Lower Extremity Arterial Disease         | 15.3 (9) | 8.2 (28)  | 6.0 (10)  | 15 (3)  | 0.23    |
| **Sociodemographic/Lifestyle risk factors** |     |           |           |         |         |
| Household Income: <$20,000/yr            | 47.9 (23) | 45.7 (122) | 36.6 (52) | 53.3 (8) | 0.23    |
| Education: any college                   | 63.0 (34) | 63.4 (203) | 65.8 (104) | 63.2 (12) | 0.69    |
| Physical activity * (µg/min), median (IQR)| 1316 (560–2236) | 1414 (616–2752) | 1428 (616–2912) | 1295 (224–2484) | 0.40 |
| Characteristics          | BMI <20 | 20 ≤ BMI < 25 | 25 ≤ BMI < 30 | BMI ≥ 30 | p-trend |
|-------------------------|---------|---------------|---------------|----------|---------|
| Alcohol consumption (3+ gl/wk) | 23.6 (13) | 26.2 (85) | 24.2 (38) | 5.3 (1) | 0.27    |
| Current Smoker (%)      | 28.8 (17) | 27.0 (93) | 15.1 (25) $^\ddagger$ | 10.0 (2) | 0.001   |

AER=albumin excretion rate  
WBC=white blood cell count

* Natural logarithmically transformed before analysis

$^\dagger$ significantly different than 20 ≤ BMI < 25 at p<0.05

$^\ddagger$ significantly different than 20 ≤ BMI < 25 at p<0.01

§ significantly different than 20 ≤ BMI < 25 at p<0.001

¶ significantly different than 20 ≤ BMI < 25 at p<0.0001
Table 2
Independent Baseline Predictors of Mortality in Type 1 Diabetes by Risk Factor Groupings in Adults ≥18 Years, Cox Regression Analyses.

|                         | Complications, base and adjusted models (n=465) | Biological Risk Factors, base and adjusted models (n=478) | SES/Lifestyle Risk Factors, base and adjusted models (n=441) |
|-------------------------|-----------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|
|                         | HR (95% CI)                                   | HR (95% CI)                                               | HR (95% CI)                                                 |
| Normal weight           | Ref                                           | Ref                                                      | Ref                                                         |
| Underweight             | 1.44 (0.79–2.63)                              | 1.60 (0.88–2.91)                                         | 1.15 (0.61–2.16)                                            |
| Overweight              | 1.13 (0.70–1.81)                              | 1.43 (0.86–2.38)                                         | 1.04 (0.58–1.86)                                            |
| Obese                   | 2.87 (1.21–6.80)                              | 3.37 (1.42–7.98)                                         | 1.15 (0.61–2.16)                                            |
| Sex (female)            | 0.69 (0.46–1.05)                              | 0.60 (0.42–0.88)                                         | 0.58 (0.38–0.88)                                            |
| Age (years)             | 2.15 (1.71–2.72)                              | 1.54 (1.16–2.04)                                         | 2.34 (1.86–2.94)                                            |
| Overt nephropathy       | 2.43 (1.52–3.74)                              |                                                          |                                                             |
| Symptomatic AN          | 2.74 (1.66–4.52)                              |                                                          |                                                             |
| Distal symmetrical PN   | 2.28 (1.42–3.66)                              |                                                          |                                                             |
| Proliferative retinopathy| 1.68 (1.02–2.77)                              |                                                          |                                                             |
| HbA1c (%)               |                                               | 1.31 (1.08–1.59)                                         |                                                             |
| AER (µg/min)*           |                                               | 1.48 (1.19–1.84)                                         |                                                             |
| Serum creatinine (mg/dl)|                                               | 1.40 (1.17–1.67)                                         |                                                             |
| Non-HDLc (mg/dl)        |                                               | 1.26 (1.06–1.49)                                         |                                                             |
| WBC (× 10³/mm²)         |                                               | 1.31 (1.12–1.53)                                         |                                                             |
| Pulse (beats/min)       |                                               | 1.34 (1.15–1.56)                                         |                                                             |
| Physical activity (kcal)|                                               |                                                          | 0.74 (0.62–0.88)                                            |
| Current smoker          |                                               |                                                          | 1.81 (1.20–2.73)                                            |
| Low income              |                                               |                                                          | 2.02 (1.33–3.06)                                            |

AN=autonomic neuropathy PN=polyneuropathy AER=albumin excretion rate WBC=white blood cell count
* natural logarithmically transformed before analyses Low income= household income <$20,000/yr

Complications model also allowed for coronary artery disease and peripheral vascular disease.
Biological risk factors model also allowed for sex, daily insulin dose/kg of body weight, high density lipoprotein cholesterol, diastolic blood pressure, use of hypertension medications, and hematocrit.
SES/Lifestyle risk factors model also allowed for having some college education, consumption of alcohol ≥3x/wk, and intensive insulin therapy.
|                       | Complications, base and adjusted models (n=519) | Biological Risk Factors, base and adjusted models (n=632) | SES/Lifestyle Risk Factors, base and adjusted models (n=598) |
|-----------------------|-----------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------|
|                       | HR (95% CI)                                   | HR (95% CI)                                               | HR (95% CI)                                                 |
| Normal weight         | Ref                                           | Ref                                                       | Ref                                                         |
| Underweight           | 2.90 (1.60–5.28)                              | 2.66 (1.46–4.85)                                          | 2.07 (1.15–3.72)                                            |
| Overweight            | 0.93 (0.57–1.49)                              | 0.72 (0.48–1.08)                                          | 0.80 (0.53–1.20)                                            |
| Obese                 | 2.00 (1.03–3.89)                              | 1.73 (0.99–3.02)                                          | 1.92 (1.07–3.44)                                            |
| Sex (female)          | 0.64 (0.42–0.97)                              | 0.58 (0.41–0.81)                                          | 0.56 (0.39–0.80)                                            |
| Age (years)           | 2.14 (1.73–2.64)                              | 1.43 (1.10–1.87)                                          | 2.16 (1.80–2.60)                                            |
| Overt nephropathy*    | 3.03 (1.86–4.95)                              |                                                           |                                                             |
| Distal symmetrical PN*| 3.33 (1.68–6.57)                              |                                                           |                                                             |
| Proliferative Retinopathy | 2.32 (1.28–4.20)                        |                                                           |                                                             |
| Peripheral vascular disease | 0.95 (0.90–1.00)                     |                                                           |                                                             |
| HbA1c (%)             |                                               | 1.40 (1.16–1.70)                                          |                                                             |
| Serum creatinine (mg/dl)** | 1.30 (1.10–1.54)                    |                                                           |                                                             |
| AER (µg/min)**        | 1.67 (1.32–2.13)                              |                                                           |                                                             |
| Non-HDLc (mg/dl)**    | 1.54 (1.28–1.84)                              |                                                           |                                                             |
| DBP (mm Hg)**         | 1.33 (1.09–1.62)                              |                                                           |                                                             |
| Hypertension medication* | 0.81 (0.74–0.88)                     |                                                           |                                                             |
| Physical activity (kcal) |                                             |                                                           | 0.64 (0.51–0.80)                                            |
| Intensive insulin therapy* |                                             |                                                           | 0.77 (0.72–0.83)                                            |
| Alcohol consumption   |                                               |                                                           | 0.93 (0.89–0.98)                                            |

*% of time with this condition AN=autonomic neuropathy PN=polyneuropathy AER=albumin excretion rate DBP=diastolic blood pressure

**natural logarithmically transformed before analyses Alcohol consumption=3+ beverages/wk Low income= household income <$20,000/yr

Complications model also allowed for coronary artery disease, proliferative retinopathy, and peripheral vascular disease.

Biological risk factors model also allowed for sex, daily insulin dose/kg of body weight, high density lipoprotein cholesterol, heart rate, and hematocrit.

SES/Lifestyle risk factors model also allowed for having some college education and years of current smoking.
Table 4

Independent Time-Varying Predictors of Mortality in Type 1 Diabetes by Risk Factor Groupings, Cox Regression Analyses.

| Complications, base and adjusted models (n=519) | Biological Risk Factors, base and adjusted models (n=632) | SES/Lifestyle Risk Factors, base and adjusted models (n=598) |
|-----------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|
| Normal weight                                 |                                                          |                                                               |
| Normal weight                                 | Ref                                                      | Ref                                                           |
| Underweight                                   | 4.28 (2.46–7.46)                                         | 3.40 (2.14–5.42)                                              | 3.01 (1.78–5.08)                                           |
| Overweight                                    | 0.81 (0.47–1.38)                                         | 0.72 (0.46–1.12)                                              | 0.85 (0.55–1.33)                                           |
| Obese                                         | 2.21 (1.26–3.88)                                         | 2.01 (1.25–3.24)                                              | 1.92 (1.18–3.14)                                           |
| Sex (female)                                  | 0.59 (0.39–0.89)                                         | 0.56 (0.39–0.79)                                              | 0.55 (0.38–0.79)                                           |
| Age (years)                                   | 2.09 (1.69–2.58)                                         | 2.10 (1.76–2.50)                                              | 2.16 (1.79–2.59)                                           |
| Coronary artery disease                       | 2.86 (1.91–4.29)                                         | 3.26 (2.06–5.17)                                              | 3.01 (1.78–5.08)                                           |
| Overt nephropathy                             | 2.08 (1.39–3.12)                                         | 2.19 (1.33–3.61)                                              | 2.06 (1.23–3.47)                                           |
| Symptomatic AN                                | 2.11 (1.41–3.14)                                         | 1.92 (1.18–3.14)                                              | 1.92 (1.18–3.14)                                           |
| Proliferative retinopathy                     | 2.33 (1.37–3.95)                                         | 1.92 (1.18–3.14)                                              | 1.92 (1.18–3.14)                                           |
| Peripheral vascular disease                   | 1.57 (1.03–2.38)                                         | 1.32 (1.14–1.53)                                              |                                                               |
| HbA1c (%)                                     |                                                          | 1.55 (1.28–1.88)                                              |                                                               |
| AER (µg/min) *                                |                                                          | 1.48 (1.31–1.66)                                              |                                                               |
| Serum creatinine (mg/dl)                      |                                                          | 1.23 (1.08–1.41)                                              |                                                               |
| Non–HDLc (mg/dl)                              |                                                          | 1.16 (1.01–1.35)                                              |                                                               |
| WBC (× 10⁹/mm³)                               |                                                          | 0.81 (0.75–0.87)                                              |                                                               |
| Physical activity (kcal)                      |                                                          |                                                               | 3.10 (2.12–4.54)                                            |
| Low Income                                    |                                                          |                                                               |                                                               |

AN=autonomic neuropathy AER=albumin excretion rate DBP=diastolic blood pressure

* natural logarithmically transformed before analyses. Low income=household income <$20,000/yr

Complications model also allowed for distal symmetrical polyneuropathy

Biological risk factors model also allowed for daily insulin dose/kg of body weight, hematocrit, high density lipoprotein cholesterol, diastolic blood pressure, use of hypertension medications, and heart rate.

SES/Lifestyle risk factors model also allowed for having some college education, low income, smoking, and consumption of alcohol ≥3x/wk.
### Table 5

Change in Body Mass Index (BMI) in Adults with Type 1 Diabetes in Follow-up Years 1–10 and Risk of Mortality in Years 11–20.

| Variable                  | HR (95% CI)       |
|---------------------------|-------------------|
| BMI change (residuals)    | 0.88 (0.80–0.97)  |
| Baseline BMI              | 1.10 (1.00–1.21)  |
| Age (years)               | 2.10 (1.53–2.87)  |
| Albumin excretion rate*   | 2.32 (1.74–3.09)  |

* Natural logarithmically transformed before analysis.

Forward selection model also allowed for sex, hypertension, HbA1c, intensive insulin therapy, HDL cholesterol, and non-HDL cholesterol.