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Risk of type 2 diabetes and cumulative excess weight exposure in the framingham offspring study★

Danielle R. Bouchard^{a,b}, Bianca Porneala^c, Ian Janssen^{d,e}, Marie-France Langlois^{f,g}, Jean-Patrice Baillargeon^{f,g}, Caroline S. Fox^{h,i}, James B. Meigs^{j,k}, Ralph B. D'Agostino Sr^l, Michael Pencina^m, and Marie-France Hivert^{f,g,j,*}

^aFaculty of Kinesiology and Recreation Management, University of Manitoba Winnipeg MB, Canada

^bHealth, Leisure, and Human Performance Research Institute, Winnipeg MB, Canada

^cNational Center for Biotechnology Information, Bethesda, MD, USA

^dDepartment of Community Health Epidemiology Queen's University, Kingston, ON, Canada

^eSchool of Kinesiology and Health Studies, Queen's University, Kingston, ON, Canada

^fDepartment of Medicine, Division of Endocrinology, Université de Sherbrooke, Sherbrooke QC, Canada

^gÉtienne-LeBel Clinical Research Center of the Centre hospitalier universitaire de Sherbrooke, Sherbrooke QC, Canada

^hFramingham Heart Study, Framingham, MA, USA

ⁱDepartment of Endocrinology, Brigham Women's Hospital, Boston, MA, USA

^jGeneral Medicine Division, Massachusetts General Hospital, Boston, MA, USA

^kHarvard Medical School, Boston MA, USA

^lBoston University Department of Mathematics and Statistics, Boston University, Boston, MA, USA

^mBoston University Department of Biostatistics, Boston University, Boston, MA, USA

Abstract

Aim—Mid-life obesity is associated with T2D risk. However, less is known about the cumulative effect of obesity during adulthood.

Methods—Framingham Offspring Study participants who had an examination at 35±2 years and were initially free of T2D were included in this study (N=1026). A cumulative excess weight (CEW) score (year*kg/m²) was calculated until T2D diagnostic or the end of follow-up.

Results—Eighty-four individuals (8.2%) developed T2D over 20±6 years. Mean CEW scores were 118.0± 114.6 year*kg/m² in individuals who developed T2D and 30.2±91.4 year*kg/m² in those who did not develop T2D (*P*<0.01). T2D risk was doubled for each standard deviation increase in the CEW score (OR= 1.99 [1.64–2.40]; *P*<0.001). However, CEW score was only

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*Corresponding author. Department of Medicine, Division of Endocrinology, Sherbrooke, QC, J1H 5N4. Tel.: +1 819 346 1110x15303; fax: +1 819 564 5292. Marie-France.Hivert@USherbrooke.ca (M.-F. Hivert).

significantly associated with T2D incidence for participants with a baseline BMI <25 kg/m² (OR =2.13 [1.36–3.36]; $P<0.001$).

Conclusions—Accumulating weight between the mid-thirties to the mid-fifties increases the risk of developing T2D. However, BMI in mid-thirties remains a stronger predictor of T2D risk.

Keywords

Adults; Aging; BMI; Diagnosis; Epidemiology

1. Introduction

The prevalence of obesity (Janssen, Shields, Craig, & Tremblay, 2010) and type 2 diabetes (T2D) (Wild, Roglic, Green, Sicree, & King, 2004) has been increasing simultaneously, in line with the fact that obesity is a strong risk factor for T2D (Centers for Disease Control & Prevention, 2004). The association between obesity and T2D risk is usually determined by assessing the body mass index (BMI) at a single point in time and determining whether this single BMI measure predicts T2D incidence (Barcelo, Gregg, Pastor-Valero, & Robles, 2007; Nyamdorj et al., 2009). A single BMI measure may be an incomplete assessment of obesity exposure status as it does not take into account how long an individual has accumulated a certain amount of excess weight.

Several studies examining the impact of obesity duration on T2D risk (Abdullah et al., 2010; Carlsson et al., 1998; Everhart, Pettitt, Bennett, & Knowler, 1992; Holbrook, Barrett-Connor, & Wingard, 1989; Sakurai et al., 1999; Wannamethee & Shaper, 1999) have generally report that the length of time a person has been obese (defined as BMI>30 kg/m²) predicts T2D risk independent of their current BMI. While the obesity duration concept offers an advantage over a single BMI measure, is still limited in that it does not consider exposure to excess weight in the overweight range (BMI=25 to 30 kg/m²). This is important because there is a graded relationship between BMI and T2D risk even in the BMI ranges below 30 kg/m² (Fox et al., 2006; Weinstein et al., 2004). Moreover, ‘obesity duration’ (number of years) does not account for the ‘degree’ of exposure, such as someone with a BMI of 45 kg/m² for 10 years is considered with a similar risk than someone with a BMI of 32 kg/m² for 10 years if ‘duration’ is the only factor.

Considering both the degree and duration of excess weight, in a manner analogous to how “pack-years” are used to assess the cumulative exposure to cigarette smoking (Mera, 2006; Wood, Mould, Ong, & Baker, 2005), may provide an even better marker of adulthood exposure to excessive weight, as suggested by others (Abdullah et al., 2010; Brancati, Wang, Mead, Liang, & Klag, 1999). Specifically, exposure to BMI values greater than the normal weight range over a prolonged period of time could be calculated to create a cumulative excess weight (CEW) score, and as a result, evaluate the risk of T2D incidence based on both degree and duration of exposure.

Based on the data from the well-characterized prospective cohort Framingham Offspring Study, the first objective of this study was to test the hypothesis that adulthood CEW score is associated with T2D incidence over a mean follow-up of 20 years. The second objective aimed to test the hypothesis that adulthood CEW score is associated with T2D incidence independent of baseline BMI.

2. Materials and methods

2.1. Data source

Our analysis was based on the Framingham Offspring Study, previously described in details (Feinleib, Kannel, Garrison, McNamara, & Castelli, 1975). Briefly, the Framingham Offspring Study is the prospective population cohort based on the offspring (and spouses) of the original Framingham Heart Study cohort, both aiming to investigate risk factors of cardiovascular diseases; data collection in the Offspring cohort started in 1971 (Dawber, 1980).

Over the prospective follow-up of the Framingham Offspring Study, examinations were performed on average over 4-year cycles. For our specific analyses, we included participants who had an examination at age 35 ± 2 years and who attended examination cycle 2 and beyond who were free of T2D at baseline. For the current study, the examination cycle completed at age 35 ± 2 years was considered the baseline for each participant. We excluded participants with T2D at baseline participants who missed two or more consecutive cycles after baseline. The overall Framingham Offspring Study population included 4676 participants. Of the initial participants, 3560 were excluded: 3355 did not cross the age of 35 during the time of our study (exam 2 or later), 209 had T2D at baseline, 9 did not have BMI data available at baseline, and 7 did not have any follow-up. Thus, 1026 participants were considered in our analyses. The study protocol was approved by the Institutional Review Boards of the Boston University Medical Center, and all participants provided written informed consent.

2.2. Exposure measurement

Body weight was measured in light clothing to the nearest 0.1 kg, while height was measured to the nearest 0.5 cm. BMI (kg/m^2) was calculated at each cycle. Standard BMI categories were used to categorize participants: normal-weight $< 24.9 \text{ kg/m}^2$, overweight = $25.0\text{--}29.9 \text{ kg/m}^2$ or obese $\geq 30.0 \text{ kg/m}^2$ (World Health Organisation, 2003). Waist circumference (WC) was measured at the level of the umbilicus to the nearest 0.1 cm. After resting for at least five minutes, a physician measured blood pressure on the left arm with a mercury-column sphygmomanometer, according to the standardized protocol (The sixth report of the Joint National Committee on prevention et al., 1997); the average of two measurements was used for analyses. Family diabetes history, defined as diabetes in one or both natural parents, was assessed by interview. Finally, plasma glucose, HDL-cholesterol, and triglycerides were measured in fasting blood samples.

The Diabetes Risk Score (DRS) was assessed using the algorithm initially developed by Wilson et al. (2007). The original algorithm was based on a maximum score of 28: (1) Fasting glucose level 100–126 mg/dL (10 points), (2) BMI $\geq 30.0 \text{ kg/m}^2$ (5 points), (3) BMI between 25.0 and 29.9 kg/m^2 (2 points), (4) HDL-C level $< 40 \text{ mg/dL}$ in men or $< 50 \text{ mg/dL}$ in women (5 points), (5) Parental history of diabetes mellitus (2 points), (6) Triglyceride level $\geq 150 \text{ mg/dL}$ (2 points), and (7) Blood pressure $\geq 130/85 \text{ mm Hg}$ or receiving treatment (2 points). To avoid redundancy in models (since the CEW score is based on BMI), the DRS was adapted by using WC instead of BMI, after consultation with the authors of the DRS (Wilson et al., 2007). As a result, WC values $\geq 102 \text{ cm}$ in men and $\geq 88 \text{ cm}$ in women replaced BMI in the algorithm with a score of 3.5. Therefore, the diabetic risk was calculated on a maximum score of 24.5 in this current study. In addition, the DRS can be calculated based on continuous variables for each component (except family history), so we performed subsidiary analyses using the DRS-continuous in the models. Adjustment for the DRS in multivariable models allowed us to account for major potential T2D risk confounders without adding many variables that would lead to instability to the models (the current

analyses including only 84 events). The DRS was developed and validated using the Framingham Offspring Study (Wilson et al., 2007); therefore, we feel confident that this score captures well the known risk factors for T2D in our sample.

2.3. CEW calculation

The Cumulative Excess Weight (CEW) score was calculated as the sum of units of BMI over (+) or under (–) the upper limit of the normal weight BMI category (25 kg/m^2) over each inter-cycle period until T2D diagnosis or the end of follow-up. To take into account the exact time between cycles, the number of days between the two cycles was calculated and then reported in years. The CEW score for each inter-cycle period was calculated as follow: $[(\text{Days between the cycle X and the cycle Y})/365.25] * [(\text{BMI at cycle X} - 25) + (\text{BMI at cycle Y} - 25)]/2$. We then summed each inter-cycle CEW value until T2D diagnostic or the end of follow-up (Fig. 1 for more details and one example). Consequently, the CEW represents the accumulation of BMI units under or above 25 kg/m^2 over time and is expressed in $\text{years} * \text{kg/m}^2$. If a subject missed a cycle, the mean BMI between the previous and the following cycle was used in the CEW calculation (for example if someone had missing BMI at exam 3, we used the average BMI between exam 2 and 4).

2.4. Outcome

The incidence of T2D was assessed in each of the 4 year follow-up cycles and was defined based on the use of diabetes medication and/ or fasting plasma glucose $\geq 7.0 \text{ mmol/L}$, as defined standardly for many other Framingham reports. The incidence of T2D over the total follow-up period was coded into a dichotomous variable (yes/no).

2.5. Statistical analysis

Baseline characteristics are presented as means ($\pm$ SD) for continuous variables or N (%) for categorical variables. Differences between participants who developed T2D and participants who remained free of T2D were assessed using Student T-tests for continuous variables and chi-square tests for categorical variables.

To test the hypothesis that adulthood CEW score was associated with T2D incidence we used two different strategies. First, the CEW score was divided into quartiles to compare T2D incidence in each quartile; other characteristics of the population were also compared per quartile of CEW (using ANOVAs). Second, the association between the CEW score and T2D incidence was assessed using logistic regression models that included age, sex, and the DRS as potential confounding factors. More specifically, we used the statistical approach of logistic regression models to estimate risk. As mentioned above, adjusting for the validated DRS score (with categorical variables) allowed us to include all major risk factors for T2D in the models without introducing instability in the models by adding many confounding variables. No difference was observed on the CEW score and BMI in final models when the DRS was introduced with continuous variables; therefore, all presented models used the DRS categorical variable. To test the hypothesis that the CEW score was associated with T2D incidence after taking into account baseline BMI, we used three different strategies. First, we used the same logistic regression model (adjusted for age, sex, and DRS) including both the CEW and baseline BMI. Second, baseline BMI was stratified by the clinical categories (normal $< 24.9 \text{ kg/m}^2$, overweight $= 25.0 - 29.9 \text{ kg/m}^2$, and obese $\geq 30.0 \text{ kg/m}^2$) to test the association between CEW and T2D incidence in each stratum of baseline BMI category. Collinearity was tested for each model and was found non-significant. Interactions between CEW and BMI (continuous or per category) were also tested. Again no significant results were observed. Finally, since participants who developed T2D had a shorter follow-up period (as expected per design, follow-up period is defined until the end of available data for individual who remained free of T2D), we did a subsidiary analysis to control for length

of follow-up using a matching strategy. Individuals who developed T2D during follow-up were matched with individuals who remained free of T2D based on follow-up period (± 2 years) in addition to sex and baseline BMI (± 1 unit). Of all cases, 62 individuals who developed T2D were matched with 191 individuals who remained free of T2D. Of the individuals that developed T2D, 12 of them could not be matched using the established criteria. P -values <0.05 were considered statistically significant. All analyses were performed using SAS software (SAS Institute, Cary, NC version 9.2).

3. Results

Of the 1026 participants included in this study (35 ± 2 years old at baseline, per design), 84 individuals (8.2%) developed T2D over a mean follow-up of 20 ± 6 years. The characteristics of individuals who developed T2D compared to individuals who remained free of T2D during follow-up are presented in Table 1. As expected, participants who developed T2D were more likely to be men, had a more adverse metabolic profile, a greater DRS, and had a more frequent family history of T2D than participants who remained free of T2D.

3.1. Association between adulthood CEW score and T2D incidence

As presented in Table 1, participants who developed T2D during follow-up had a CEW score that was almost four times greater than participants who remained free of T2D (118.0 ± 114.6 vs. 30.2 ± 91.4 year*kg/m²; $P < 0.001$). T2D incidence increased gradually among CEW quartiles with the highest incidence in the fourth quartile (0.4%, 4.3%, 8.6%, and 19.5% respectively; $P < 0.001$; see Table 2). Baseline BMI also increased across CEW quartiles (20.8 kg/m², 23.6 kg/m², 26.0 kg/m² and, 30.3 kg/m² respectively; $P < 0.001$) as did all of the metabolic variables (Table 2).

We evaluated the association between CEW score and T2D incidence while adjusting for main T2D risk factors. The CEW score was significantly associated with the risk of developing T2D independent of age, sex, and the DRS (per categorical or continuous variables). Specifically, the odds ratio (95% CI) per each standard deviation increase in the CEW was 1.99 (1.64–2.40; $P < 0.001$).

3.2. Association between adulthood CEW score and T2D incidence adjusted for baseline BMI

Baseline BMI was significantly associated with the risk of developing T2D when adjusted for age, sex, and the DRS (OR=2.42 per SD increase [95% CI =1.97–2.97]; $P < 0.001$). In the logistic regression analysis that included both the baseline BMI and the CEW score, baseline BMI remained significantly associated with T2D incidence (OR=1.80 [1.27–2.47]; $P < 0.001$) but the CEW did not (OR=1.00 [0.71–1.42]; $P=.93$) (see Table 3).

The ORs derived from the logistic regression analyses were stratified by baseline BMI categories to assess the association between CEW and T2D incidence in each group. For individuals who were categorized as normal weight (< 24.9 kg/m²) in their mid-thirties, the CEW score was significantly associated with T2D incidence (OR= 2.13 [1.36–3.36]; $P < 0.001$) when adjusted for age, sex, and the DRS. The CEW score was not significantly associated with T2D incidence in individuals who were overweight [OR=1.25 (0.88–1.77)] or obese [OR=0.96 (0.65–1.42) at baseline (Table 3).

Finally, 62 individuals who developed T2D were paired to 191 individuals who remained free of T2D matched based on length of follow-up, sex, and baseline BMI. In this subsidiary analysis, individuals who developed T2D had a CEW score of 94.9 ± 78.3 year*kg/m² compared to 63.6 ± 87.5 year*kg/m² ($P=0.01$) for the matched controls.

4. Discussion

The degree and duration of excess BMI from the mid-thirties to the mid-fifties, as captured by the CEW, were associated with T2D incidence in the Framingham Offspring Study. When baseline BMI (measured at ~35 years) and the CEW score were considered in the same model, only baseline BMI remained significantly associated with T2D incidence. However, the CEW score was significantly associated with T2D incidence among individuals who were in the normal weight range initially (baseline BMI <25 kg/m²). In addition, in our subsidiary analyses where baseline BMI and follow-up time were matched, the CEW was significantly higher in individuals who develop T2D.

Our approach for evaluating the impact of the cumulative exposure to excessive body weight on T2D risk is novel and differs from other studies that have reported the impact of obesity at one point in time (Barcelo et al., 2007; Leibson et al., 2001; Nyamdorj et al., 2009) or obesity duration (Carlsson et al., 1998; Everhart et al., 1992; Holbrook et al., 1989; Pontiroli & Galli, 1998; Sakurai et al., 1999; Wannamethee & Shaper, 1999). Previous studies assessing obesity duration mainly determined the numbers of years participants had a BMI above 30 kg/m². Our CEW approach refined this concept by accounting for any excessive weight above a BMI of 25 kg/m² (not only when BMI reaches 30 kg/m²), the degree of exposure (as the number of units away from a BMI of 25 kg/m²), and the duration of this excessive weight. This method provides a more complete assessment of exposure to excess weight because overweight status and modest weight gain below the obesity threshold are associated with T2D risk (Weinstein et al., 2004); (Colditz, Willett, Rotnitzky, & Manson, 1995), and because it accounts for the effects of weight variations on risk (Guagnano et al., 2000; Marchesini et al., 2004; Venditti, Wing, Jakicic, Butler, & Marcus, 1996).

Recently, Lee, Gebremariam, Vijan, and Gurney (2012) investigated the impact of excess weight accumulation using a similar excess weight cumulative score to that used in our study, but within a younger cohort followed from age 14–21 until early adulthood. In line with our results, they found that excess weight accumulation was associated with an increased risk of T2D in early adulthood. Our study adds to these data by exploring risk of T2D associated with excessive weight exposure in an older age range population. In the Lee et al. report, excessive weight exposure from adolescence to adulthood was more associated to T2D incidence than baseline BMI (self-reported). In our analyses, baseline BMI was more strongly related to T2D incidence than the CEW when both variables were considered in the same regression model. However, within the subsidiary analysis that matched for baseline BMI and length of follow-up, the CEW was 21% lower in the participants who remained free of T2D over 16 years. The different findings for these two analyses indicate that the longer period of follow-up in participants who remained free of T2D might have obscured the association in the logistic regression based on the overall population because of the nature of the statistical approach we used initially. Therefore, the matched analyses seemed more appropriate since it takes into account length of follow-up that had the potential to significantly influence the CEW. Another important difference between our data and those of Lee et al. (2012) is the actual baseline obesity status of the individuals in the two populations, theirs being composed mainly (96%) of normal weight individuals at baseline (Lee et al., 2012). In line with this observation, we found that the CEW was associated with risk of T2D in individuals who were normal weight at baseline around 35 years of age. Because such association was not observed for overweight and obese individuals, this suggests that being overweight or obese at 35 years is a strong risk factor for development of T2D and that effort of prevention of weight gain could target individuals before they reach their mid-thirties. It is also possible that calculating the CEW score from early adulthood up to 35 years old would be of importance in individuals that are overweight or obese at age 35 (our baseline). We acknowledge that the optimal baseline time point to calculate the

‘exposure’ to excess weight might be earlier than 35 years old, but this would have greatly limited the number of individuals included in this study.

Of note, our results do not mean that further weight gain in overweight and obese middle-age adults is not harmful for other obesity-related conditions such as osteoarthritis, sleep apnea or functional limitation (Bray, 2004). Attempts to lose weight should still be encouraged for overweight or obese patients since it is now well established that a lifestyle intervention resulting in slight weight loss (4%–7%) can reduce T2D incidence by up to 58% (Knowler et al., 2002; Lindstrom et al., 2003). Moreover, other studies have demonstrated that weight fluctuation *per se* (Hanson et al., 1995) was not associated with increased T2D risk.

4.1. Strengths and limitations

Our study has many strengths, including the use of a well-characterized prospective cohort study with objective and standardized measurements of exposures confounders, and outcomes over a period of 20 years. The large number of participants in the Framingham Offspring Study allowed us to select a homogeneously-aged sample with assessment starting in the mid-thirties. However, some limitations need to be mentioned. First, voluntary or involuntary reasons for body weight fluctuation were not measured. Baseline BMI and CEW score were strongly correlated ($r=0.82$; $P<0.001$) possibly introducing colinearity in the models and partly explaining why only one remained statistically significant when both were included directly in the same logistic regression model. Second, the CEW is dependent of follow-up period. Third, it is possible that some misclassification of the outcome occurred due to the variation in the T2D definition. Finally, because the Framingham Offspring Study is composed of individuals who were mainly of European descent, our findings may not be generalizable to other ethnic groups.

In conclusion, we demonstrated that a score capturing the degree and the duration of cumulative excessive weight between mid-thirties to mid-fifties was associated with increased risk of developing T2D. However, BMI in mid-thirties remains a stronger predictor of T2D risk. Our results underline the importance for primary prevention to prevent excess weight accumulation in normal-weight individuals early in the adulthood period.

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Figure 1.

An example of how CEW was calculated. The CEW between two cycles was calculated as:

$[(\text{Days between cycle X and cycle Y} / 365.25)] * [(\text{BMI at cycle X} - 25) + (\text{BMI at cycle Y} - 25)] / 2$. The total CEW score was calculated by summing the CEW scores calculated between the different cycles. Fig. 1 shows an example for one participant: $\text{CEW} = [1452 \text{ days} / 365.35] * [(26.1 - 25 + 27.3 - 25) / 2] + [1460 \text{ days} / 365.35] * [(27.3 - 25 + 24.2 - 25) / 2] + [1449 \text{ days} / 365.35] * [(24.2 - 25 + 22.1 - 25) / 2] + [1450 \text{ days} / 365.35] * [(22.1 - 25 + 28.5 - 25) / 2] + [1451 \text{ days} / 365.35] * [(28.5 - 25 + 29.2 - 25) / 2]$. $\text{CEW} = 6.75 + 5.99 - 7.34 + 1.19 + 15.28$, $\text{CEW} = 21.87 \text{ year} * \text{kg/m}^2$.

Table 1

Description of the cohort.

	Control (n=942)	T2D (n=84)	P-values
	Mean±SD or N (%)		
<i>Baseline Characteristics</i>			
Age (at baseline, per design)	35.0±1.3	35.2±1.3	0.25
Men, N (%)	424 (45.2)	50 (58.6)	0.04
BMI (kg/m²)	24.8±4.2	29.9±6.0	<.001
Waist circumference (cm)	84.8±13.7	102.1±15.0	<.001
Fasting glucose (mg/dL)	90.2±8.7	99.0±9.8	<.001
High-density lipoprotein (mg/dL)	50.4±13.08	39.8±11.6	<.001
Triglycerides (mg/dL)	189.4±165.6	341.8±365.3	<.001
Systolic blood pressure (mmHg)	113.7±12.7	122.3±13.6	<.001
Family history of diabetes, N (%)	164 (17.4)	33 (38.1)	<.001
Diabetes Risk Score ^a	5.3 (5.1)	12.9 (6.3)	<.001
<i>Follow-up Characteristics</i>			
Length of follow up (years)	20.2±5.7	16.8±6.6	<.001
Age (T2D or end of follow-up)	55.2±5.9	52.1±6.7	<.001
BMI (kg/m²) (T2D or end of follow-up)	28.8±5.3	35.2±6.8	<.001
Cumulative Excess Weight (CEW) score (year*kg/m²)	30.2±91.4	118.0±114.6	<.001

T2D: type 2 diabetes; BMI: body mass index.

^aDiabetes Risk Score calculated according to Wilson et al. (2007) and modified by use of waist circumference instead of BMI in the calculation.

Table 2

Subject characteristics by cumulative excess weight quartiles.

Cumulative Excess Weight (CEW) quartiles	Q1 (n=257)	Q2 (n=256)	Q3 (n=257)	Q4 (n=256)	P value
Mean year ^a kg/m ² ±SD:	-64.5±30.6	-0.8±13.0	49.6±16.1	165.5±86.8	
Range:	-172.5 to -24.6	-24.3 to 22.8	23.1 to 80.5	80.5 to 599.4	
Mean±SD or N (%)					
Baseline					
Men, N (%)	51 (19.8)	122 (47.7)	156 (60.7)	148 (57.8)	<.001
BMI (kg/m ²)	20.8±1.6	23.6±2.0	26.0±2.8	30.3±4.5	<.001
Waist circumference (cm)	72.6±8.1	81.8±9.7	89.7±10.7	101.1±12.7	<.001
Fasting glucose (mg/dL)	87.4±8.2	90.87±8.7	91.3±9.6	94.1±8.8	<.001
High-density lipoprotein (mg/dL)	56.8±12.2	49.8±12.9	46.9±13.3	44.8±11.5	<.001
Triglycerides (mg/dL)	149.9±115.1	177.6±138.7	216.4±226.3	263.7±245.8	<.001
Systolic blood pressure (mmHg)	109.9±11.7	112.8±13.8	115.4±11.4	119.5±13.1	<.001
Family history of diabetes, N (%)	39 (15.2)	41 (16.0)	56 (21.8)	60 (23.4)	0.03
Diabetes Risk Score ^a	3.4±4.1	4.8±4.9	6.2±5.8	9.2±5.8	<.001
Follow-up					
Length of follow-up (years)	21.5±4.3	17.7±7.3	19.6±5.7	21.0±5.0	<.001
Diabetes incidence in each quartile, N (%)	1 (0.40)	10 (4.3)	22 (8.6)	50 (19.5)	<.001

BMI=body mass index.

^aDiabetes Risk Score calculated according to Wilson et al. (2007) and modified by use of waist circumference instead of BMI in the calculation.

Table 3

Risk of type 2 diabetes determined by CEW.

	OR (95% CI)	P value
Model 1	1.99 (1.64–2.40)	<.001
Model 2	1.00 (0.71–1.42)	.76
Analyses by BMI stratum adjusted for sex and DRS		
BMI <25.99	2.13 (1.36–3.36)	<.001
BMI 25– 29.99	1.25 (0.88–1.77)	.21
BMI 30.00	0.96 (0.65–1.42)	.83

Model 1 was adjusted for sex and the Diabetes Risk Score (DRS).

Model 2 was further adjusted for BMI.